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INTRACRANIAL VASCULAR LESIONS IN LATE RHEUMATIC HEART DISEASE

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ANATOMIC studies of the brain were long neglected in cases of chronic rheumatic heart disease. It is only during the last fifteen or twenty years that a number of papers dealing with this aspect of the rheumatic state have been published. Bodechtel [1] saw intimal proliferation in meningeal vessels in a case of chronic relapsing endocarditis. Von Sántha [2] studied a case of rheumatic chorea and found thrombosis with organization and occasionally also intimal proliferation and endothelial exfoliation. Productive endarteritic lesions were also present in the cortical capillaries and precapillaries and were sometimes associated with fibrinoid imbibition of their walls. The significance of such lesions in the genesis of chorea was more recently discussed by Buchanan, Walker and Case.[3] Similar changes already had been observed by Winkelman and Eckel [4] in 5 brains, which, however, came from patients with acute rheumatic fever. Kernohan, Woltman and Barnes [5] described thrombotic and embolic lesions of small vessels in 23 cases, in most of which these lesions were associated with chronic rheumatic endocarditis. Lindsey [6] described a case of ruptured rheumatic aneurysm of the posterior inferior cerebellar artery. Dublin [7] found proliferative and thrombotic occlusions of vessels of various sizes in psychotic patients with chronic rheumatic heart disease. Recently Benda [8] observed similar changes in the brains of mentally defective children. The most important papers dealing with the late intracranial sequelae of rheumatic fever are those of Bruetsch.[9] He stated that obliterative

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1. Bodechtel, G.: Ztschr. f. d. ges. Neurol. u. Psychiat. **140**:657, 1932.
2. von Sántha, K.: Virchows Arch. f. path. Anat. **287**:405, 1932.
3. Buchanan, D. N.; Walker, A. E., and Case, T. J.: J. Pediat. **20**:555, 1942.
4. Winkelman, N. W., and Eckel, J. L.: Arch. Neurol. & Psychiat. **28**:844, 1932.
5. Kernohan, J. W.; Woltman, H. W., and Barnes, A. R.: Arch. Neurol. & Psychiat. **42**:789, 1939.
6. Lindsey, S.: J. Nerv. & Ment. Dis. **99**:717, 1944.
7. Dublin, W. B.: Dis. Nerv. System **2**:390, 1941.
8. Benda, C. E.: J. Nerv. & Ment. Dis. **106**:84, 1947.
9. Bruetsch, W. L.: J. A. M. A. **134**:450, 1947.

endarteritis of leptomeningeal vessels, with resulting gross and microscopic infarctions of the gray matter, is comparatively frequent. The relation of such lesions to psychiatric problems was considered by Bruetsch, and more recently, by Van der Horst [10] and by Rojas and Vila.[11] The studies of Bruetsch were concerned exclusively with psychiatric patients. We felt that additional studies of the brain in unselected cases of chronic rheumatic heart disease were desirable. In a series of 688 consecutive autopsies there were 45 in which rheumatic heart disease was noted in patients older than 25 years, excluding those in whom it was complicated by subacute bacterial endocarditis. The brain was adequately examined in 14 of these cases, and in 9 it showed significant vascular changes.

Our series was not large enough to provide statistically reliable data on the incidence of cerebral lesions; however, we obtained the impression that in the majority of cases of chronic rheumatic heart disease vascular changes within the cranial cavity can be found readily by careful routine examination.

REPORT OF CASES

Case 1.—A white woman of 34 years stated that she had had rheumatic heart disease and chorea at the age of 8. During the year prior to consultation she had epileptiform seizures, and for six months she had noted dysphagia, dysphasia, paresthesias of the arms, unequal pupils, and mental deterioration. She lost consciousness unexpectedly, pulmonary edema developed and she died.

The heart weighed 300 Gm. and showed severe mitral stenosis. All arteries, including those of the brain, were delicate and patent. Scattered areas of softening were present in the inferior portion of the right temporal, parietal and occipital cortex and the subjacent white matter. Several convolutions of the lateral portion of the right frontal lobe and the base of the left frontal lobe were firm, brown or yellow, and narrowed. The right lenticular nucleus showed anemic softening, and the left was cystic. The brain stem was intact. The basal arteries showed concentric and circumscribed webby fibrocellular proliferations of the intima, swollen elastic membranes and patent lumens. A small vein in the cortical softening contained a nodular dense fibrous and cellular intimal projection; another vein was thickly incased by dense collagen, and a third was filled by a laminated thrombus.

Case 2.—In a white woman of 49 years acute polyarthritis developed two weeks after an attack of severe tonsillitis. The heart then gave evidence of fibrillation and decompensation. The patient became delirious. Her blood pressure was 175 systolic and 120 diastolic. The duration of the previous rheumatic heart disease was unknown.

The heart weighed 670 Gm. The mitral valve was dilated, and the cusps were thickened and bore verrucae. The aortic valve was moderately fibrosed. A thrombus was present in the right atrial appendage. There was active rheumatic myocarditis. The systemic arteries showed little sclerosis; the vessels of the brain were delicate. A typical area of "granular atrophy" of the second and third con-

10. Van der Horst, L.: Digest of Neurol. & Psychiat. **15**:399, 1947.

11. Rojas C., A., and Vila S., G.: Rev. chilena de neuropsiquiat. **1**:133, 1947.

volutions of the right frontal lobe measured 3 by 2 cm. There was a small old infarct in the right postcentral region. The small leptomeningeal arteries and venules of the affected area were thin walled, but the lumens were filled with acellular fibrillar connective tissue that had proliferated from the intima; loose adventitial connective tissue was abundant. Some superficial cortical capillaries were distended by homogeneous acidophilic material.

Case 3.—A hypertensive white woman of 70 years died three weeks after suffering right hemiplegia. Rheumatic heart disease had not been diagnosed.

The heart was somewhat enlarged and slightly dilated. Moderate mitral stenosis with focal calcification and slight aortic valvular fibrosis were present. Other findings included mild coronary and aortic sclerosis and severe arterial and arteriolar nephrosclerosis. The vessels of the brain were practically free from sclerosis. A well defined, almost cystic infarct occupied the left parietal white matter, a part of the frontal lobe and the internal capsule. The middle cerebral artery contained a spongy fibrinous thrombus which enmeshed a few foam cells, was covered by endothelial cells and was attached by narrow strands to the intima in many places. The intima consisted of a narrow strip of fibrous tissue with few nuclei. The thickened homogeneous internal elastic membrane was superficially jagged. The media was diffusely fibrosed. The adventitia was slightly to moderately thickened and poorly nucleated.

Case 4.—A white 39 year old woman had eclampsia and left hemiplegia nine years prior to consultation. She recovered from the paralysis, but it recurred two years ago. After that she had many epileptiform seizures. Death occurred five days after a third cerebrovascular accident. Presumably she had rheumatic fever without involvement of joints in childhood. The blood pressure was elevated.

The heart weighed 320 Gm. and showed chronic verrucous endocarditis and severe mitral stenosis. There was also myocardial and renal rheumatic vasculitis. The brain showed an old cystic infarct of the right frontoparietal area and a recent infarct of the left parietal lobe. The cerebral vessels were delicate, but the left middle cerebral artery was occluded by a soft thrombus. Histologically, the thrombus was a meshwork of fibrin covered by endothelium-like cells and attached to points of focal intimal thickening. Cellular and fibrous papillary nodules projected into the lumens of the larger vessels from the intima; the internal elastic membrane was swollen, irregular and split. The other arteries showed loose webby connective tissue filling the lumens, irregularity of the elastic membranes and hyaline thickening of the adventitia. One large artery was filled by a cellular-fibrous, extensively recanalized thrombus. The media was intact. Small arteries and veins in the area of the recent infarct showed intact intima but great compression of the media by hyalinized adventitia. Some of these vessels were also filled by loose connective tissue. Intracortical precapillaries with swollen endothelial and adventitial cells contained homogeneous fibrin-like masses in their lumens.

Case 5.—A Mexican man of 60 years entered the psychopathic hospital because of recent persecutory delusions, assaultiveness and irritability. He had undergone three cerebrovascular accidents in the last three years, resulting in right hemiplegia. He died in cardiac failure, but rheumatic heart disease was not suspected.

The heart weighed 600 Gm. The aortic leaflets were fused, thickened and nodularly calcified. The free margin of the mitral valve was slightly thickened. The coronary arteries and the aorta were moderately sclerotic. The vessels of the brain were thin walled with smooth intima. A thrombus occluded the left middle cerebral artery. A softening of the left parietal lobe extended into the frontal and temporal lobes. This lesion appeared to be superimposed on an older cystic infarct.

The left half of the pons and the medulla was atrophied. The basal vessels showed diffuse concentric fibrous and cellular thickening of the intima with occasional focal mucinous areas and thick collagen bundles. The internal elastic membrane was thickened, glassy and homogeneous. A papillary, cushion-like intimal thickening projected into the lumen of the left middle cerebral artery, which also contained a recent porous fibrin thrombus. The media of this vessel, in part, was diffusely fibrosed and poorly nucleated. The adventitia of the veins was greatly thickened, and the endothelium was intact.

Case 6.—A white man of 46 years had suffered from rheumatic heart disease for thirty-two years. Death followed the amputation of one leg because of embolic gangrene. There had been no symptoms referable to the brain.

The heart weighed 495 Gm. Both the aortic and the mitral valve were severely stenosed, and mural thrombi were present in both atriums. The cerebral vessels were grossly intact; a small scar was present in the cerebellar cortex. The large and small arteries of the thickened, edematous leptomeninges of the parietal lobe had numerous nodules protruding into their lumens. The lesions were composed of compact fibroblasts and some macrophages, were covered by endothelium and contained occasional capillary channels. Stains for elastic tissue revealed the formation of elastic laminas within the nodules. With the Van Gieson stain the nodules were yellow, and none contained collagen. The lumen of an occasional arteriole was completely blocked by hyaline thrombotic material, and the walls of some of the arterioles showed a mild increase in both collagenic and elastic fibers. The markedly thickened adventitia of a few vessels, together with the abundant perivascular connective tissue, contained proliferative fibroblasts and a moderate number of infiltrating lymphocytes with a few polymorphonuclear leukocytes. Several small arteries contained spherical acidophilic acellular nodules; these rested on thin intact intima, were free of elastic fibers and were covered by endothelium. Focal areas of the subjacent cortex were rarefied, depleted of neurons and contained gitter cells. In the cerebellar scar the folia were shrunken; most Purkinje and granular cells were absent; the Bergmann cell layer was spared.

Case 7.—The heart of a white man of 60 years became progressively decompensated for one month, and he expectorated blood-tinged sputum during his last four days. Death was due to generalized miliary tuberculosis and rheumatic heart disease. The heart weighed 510 Gm.; the mitral valve was severely stenotic, and the cusps bore bland vegetations. There was mural thrombosis of the left atrium. The systemic arteries showed minimal sclerosis; the vessels of the brain showed none at all. Several small leptomeningeal arteries and a vein, each with intact walls, contained partially obstructive homogeneous acidophilic masses covered by flat endothelium-like cells. The wall of a large vein possessed greatly thickened fibrous adventitia and intact endothelium. The cortical cells showed ischemic changes. Tuberculous lesions of the central nervous system were absent.

COMMENT

The vascular lesions observed in our cases may be summarized as follows: The vessels chiefly involved were the small, medium-sized and larger basal arteries and also the veins of the leptomeninges. In 3 cases the lumen of a large vessel contained, but was not completely obstructed by, a spongy polypoid thrombotic mass made up predominately of fibrin and covered by a layer of flat endothelial cells. Thrombi of this type sometimes showed admixture of erythrocytes and small

collections of foam cells. Unlike the thrombi typically seen in other conditions, these resembled the cardiac valvular vegetations that are present in rheumatic endocarditis. At the points of their attachment to the intima, endothelial lesions were minimal or absent in some cases, but in others there were circumscribed cellular-fibrous intimal thickenings. In addition to the massive thrombi, small solid sessile thrombi were observed, predominately in smaller vessels. In later stages these small thrombi were converted into richly cellular nodules with occasional elastic fibers and capillaries, but without collagen. Apart from thrombosis, there was apparently independent intimal proliferation of fibroblasts and fibers arranged in a loose webby fashion; mucinous foci and occasional collagenic bundles showing fibrinoid degeneration were present. This endarteritic process usually left the lumen patent but in a single instance produced complete obstruction with recanalization. It is open to question whether the rarefied appearance of the intimal and luminal connective tissue might be the final outcome of resorption of hyaline or lipoid material, similar to the process described by Scholz and Nieto [12] in hyalinosis of cerebral arterioles. The internal elastic membrane was constantly altered, showing homogeneous thickening, splitting and disruption, and superficial jagged indentations. The media showed fibrosis with close intermingling of the collagen and smooth muscle fibers. The adventitia was thickened frequently, owing to overgrowth of collagenic tissue.

An important question is whether the thrombi mentioned previously have always formed in situ or whether some of them are embolic. In all of our cases there were old valvular lesions: in some, recurrent mitral vegetations, and in 2, mural thrombi in the left cardiac chambers. There was embolism of the lower extremity in 1 instance. At first sight this might suggest an embolic genesis of the cerebrovascular occlusions. It is doubtful, however, whether firmly adherent valvular vegetations of chronic rheumatic heart disease ever become embolized. Probably emboli from mural thrombi would block larger vessels, causing complete occlusion. It would appear, therefore, that masses of fibrin seen in smaller vessels, as in our cases, are thrombotic rather than embolic. This conclusion is supported by their attachment to vessel walls only in circumscribed areas and by their incomplete obstruction of the lumen. Frequently, one gets the impression that the larger thrombi mushroom from a comparatively minute point or points of intimal attachment. In their histologic structure also they differ from emboli, because they consist predominantly of a fibrin meshwork with a paucity of cellular elements rather than being solid laminated thrombi. The genesis of the

12. Scholz, W., and Nieto, D.: Ztschr. f. d. ges. Neurol. u. Psychiat. **162**:675, 1938.

process, in accordance with the views of Roessle,[13] may have been as follows: The subendothelial connective tissue underwent fibrinoid swelling, the endothelial layer was loosened and broken away from its

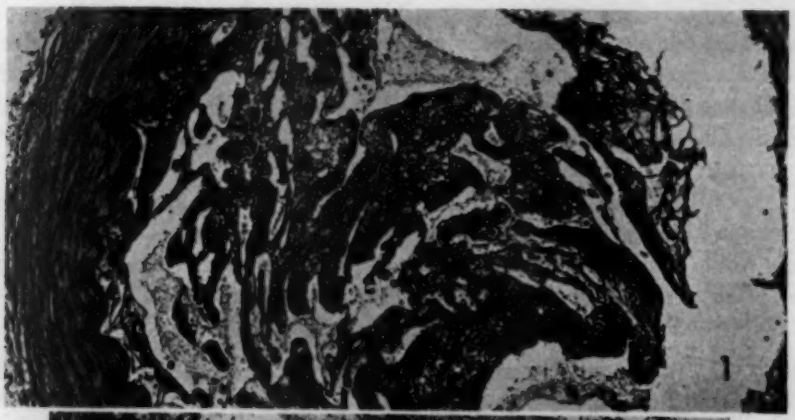

Fig. 1.—Loosely attached polypoid thrombus in a large artery. × 55.

Fig. 2.—Recent mural fibrinous thrombus and an intimal hillock, possibly an organized thrombus. × 60.

base, plasma and cellular elements from the lumen were pressed in, and thus a subendothelial cushion was formed. It is possible that the gaps

13. Roessle, R.: Virchows Arch. f. path. Anat. **288**:780, 1933.

between the endothelial layer and the remainder of the vessel wall, frequently seen in our cases, were not, or were not necessarily, artefacts but were rather an intravital process identical with Roessle's "decolla-

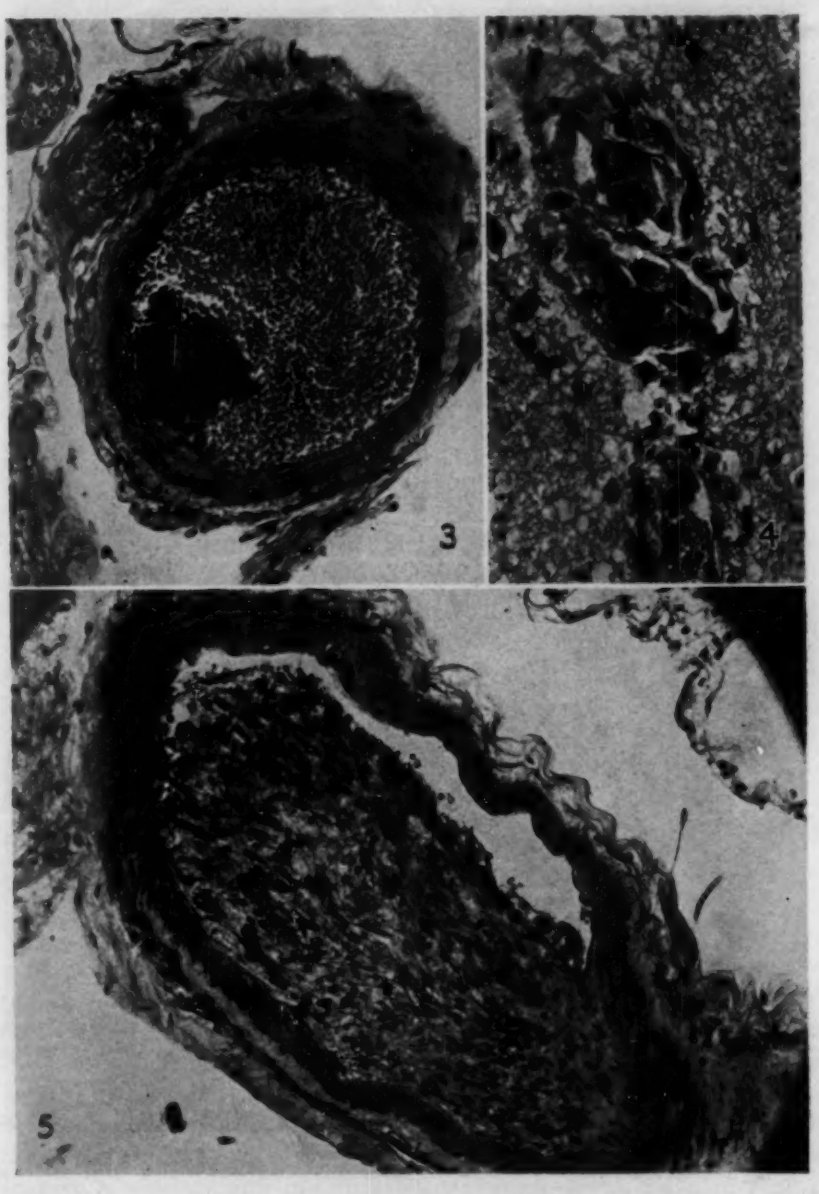

Fig. 3.—Discrete mural thrombus in a small leptomeningeal artery. × 200.

Fig. 4.—Thrombosis of intracortical precapillaries. × 325.

Fig. 5.—Subtotal obliteration of the lumen by an organized thrombus or possibly an intimal proliferation. × 150.

tion and desmolysis." The adventitia often showed fibrous thickening, occasionally of a high degree and associated with compression of the media.

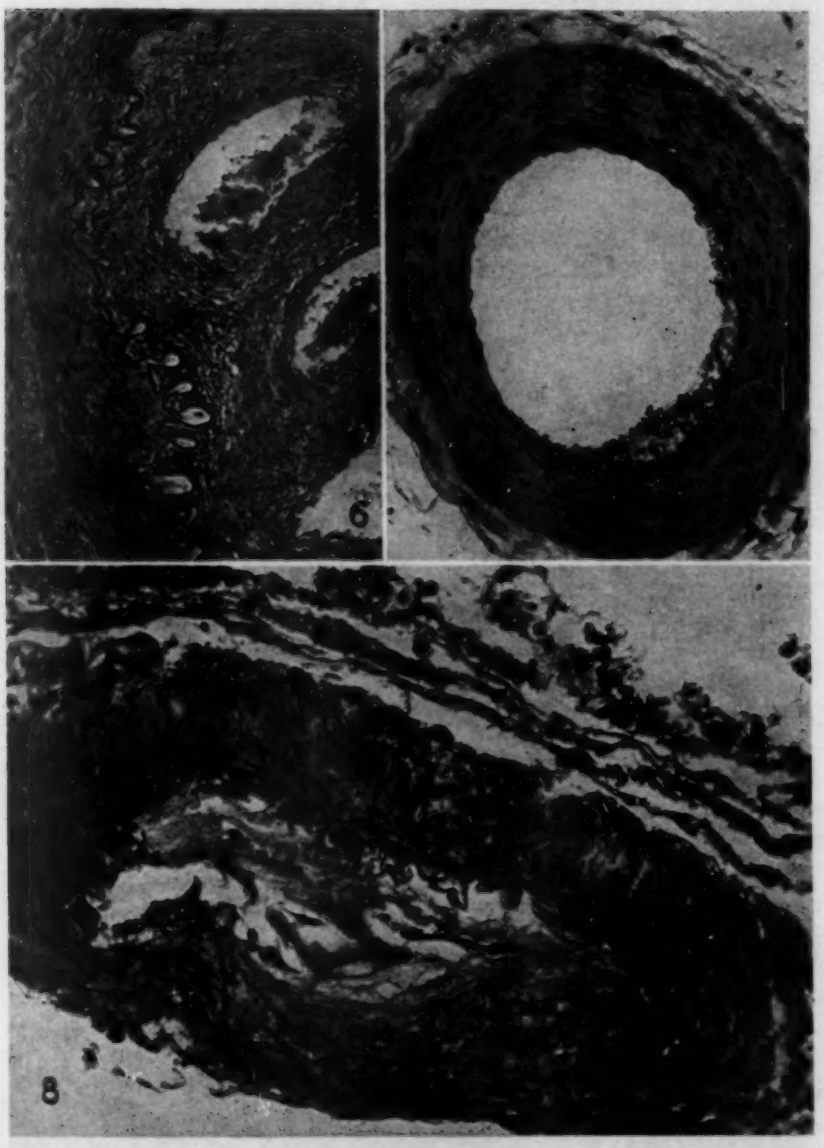

Fig. 6.—Recanalization of connective tissue filling the lumen of a large artery; fibrosis of outer coats. × 125.

Fig. 7.—Endarteritis with concentric intimal proliferation. Note the internal elastic membrane and the thin media. × 180.

Fig. 8.—Small artery with loose connective tissue filling the lumen and with adventitial fibrosis. × 175.

The lesions of the nervous parenchyma secondary to the vascular alterations were not essentially different from those produced by other forms of circulatory disturbance and will not be discussed. All lesions from minute cerebral infarcts and scars to large softenings with formation of cysts were observed, and the occurrence of so-called granular atrophy of the cortex is probably not infrequent.

The differentiation of vascular lesions associated with the late stage of rheumatic heart disease from other vascular lesions found in the cranial cavity requires discussion. The rheumatic alterations histologically are not like those of arteriosclerosis. Arteriosclerosis was grossly absent in every case. The peculiarities of the thrombi, the lack of atheromatous plaques and the presence of greatly thickened adventitia are other distinguishing features.

"Obliterative cerebral arteriosclerosis" as described by Scheinker [14] shows "tremendous expansion of the intima resulting in narrowing or complete obliteration of the vessel lumen." The absence of endothelial proliferation and of fibrin plugs distinguishes this condition from rheumatic lesions, according to Scheinker.

Vascular lesions of thromboangiitis obliterans (Buerger's disease), which in rare instances may involve the central nervous system, may be similar to some of the rheumatic manifestations; however, in such cases the absence of rheumatic heart disease and the presence of Buerger's disease elsewhere would be distinguishing.

Cerebrovascular lesions found in hypertension, even without arteriosclerosis, consist of loosening, edema, fatty metamorphosis, partial necrosis, fibrosis and hyaline degeneration of the arteriolar walls of the brain and the meninges.

In syphilis the intimal proliferation commonly is accompanied by adventitial inflammation or even lymphocytic infiltration of all layers; thrombi are absent.

In periarteritis nodosa the essential findings are heavy segmental inflammation, intimal and medial fibrinoid degeneration and necrosis, and perivascular fibrosis.

While, therefore, the vascular changes in the meninges and the brain accompanying rheumatic heart disease appear to be different from those in other conditions, occasional diagnostic difficulties will be encountered if the microscopic picture alone is considered. The "specificity" of those lesions is debatable. Because the human body has at its disposal a limited number of tissue reactions that may be elicited by a host of causative agents, it is not surprising that almost identical histologic changes occur in etiologically different conditions. It is often impossible to give a succinct and incontestable statement as to the nature of a

14. Scheinker, I. M.: Am. J. Path. **22**:565, 1946.

lesion solely on the grounds of the histologic structure, without knowledge of the over-all findings in the respective case. It follows that some of the vascular lesions described may occur in other conditions, too, but they dominate the picture in such a "characteristic" if not "specific" way in cases of rheumatic heart disease that they may be designated as rheumatic lesions. Therefore, the term "rheumatic brain disease" as employed by Bruetsch appears justified.

We have expressed our belief that while most of the vascular lesions are due to thrombosis and organization, undoubtedly there are others that are characterized by independent endarteritic proliferation. In early stages the differentiation is easy. In late stages it is sometimes impossible to decide whether the plug filling the lumen is the result of organization of a thrombus or the result of endarteritis. This difficulty was also encountered by Lindenberg and Spatz [15] in their attempt to explain the genesis of the arterial lesions of Buerger's disease involving the brain.

The cerebrovascular condition was a decisive factor in causing death in 2 patients, both of whom had hypertension. The presence of hypertension failed to manifest itself in characteristic cerebrovascular lesions, and consequently hypertension was not considered the important pathogenic factor. In other cases, the brain lesions were incidental observations at autopsy, or were observed only microscopically. In the majority of cases, death was due to the cardiac sequelae of rheumatic heart disease.

Most of the vascular lesions described, particularly the thrombi, appeared to be fairly recent. Their development in late stages of exceedingly chronic rheumatic heart disease, comparable to the events in syphilis, can be understood only when the cause of rheumatic fever is clarified. It is possible that deterioration of circulation in the final stages of cardiac failure favors the development of the lesions. The medial fibrosis is probably the outcome of an older process; it may be related to scars in the media of other vessels as described by Von Glahn and Pappenheimer,[16] Klinge and Vaubel,[17] and others. The late lesions are different from those described in cases of more acute rheumatic disease, in which cortical capillary endangiitis (Winkleman and Eckel [4]) and hyalinization of intracerebral vessels, adventitial fibrosis and perivascular fibrocytic nodules in meningeal vessels (Neubuerger [18]) may occur; the only finding common to acute and chronic stages is adventitial fibrosis. All features observed are consistent with the various forms of "acute inflammations of arteries" that were described by

15. Lindenberg, R., and Spatz, H.: Virchows Arch. f. path. Anat. **305**:531, 1940.
16. Von Glahn, W. C., and Pappenheimer, A. M.: Am. J. Path. **2**:235, 1926.
17. Klinge, F., and Vaubel, E.: Virchows Arch. f. path. Anat. **281**:701, 1931.
18. Neubuerger, K. T.: Dis. Nerv. System **8**:259, 1947.

Karsner [19] as occurring in the course of rheumatic fever, as well as with lesions of myocardial vessels seen in active and inactive forms of the disease by Gross, Kugel and Epstein.[20] However, they are not identical with the typical inflammatory picture of generalized rheumatic arteritis (Von Glahn and Pappenheimer [16]; Klinge and Vaubel [17]).

With regard to the clinical significance of the vascular lesions we should like to make the following statement: Focal neurologic symptoms will occur when the vascular changes are sufficiently developed to cause circulatory disturbances in important areas. Infarctions, softening cysts, and granular atrophy may or may not manifest themselves clinically; this will depend on the number and location of the destroyed areas in the parenchyma in a given case. We believe that the lesions under discussion are not the anatomic basis for psychoses, particularly schizophrenia. Lesions absolutely identical with those described by Bruetsch may be found in both psychotic and nonpsychotic patients. Whether a patient with such lesions becomes schizophrenic or epileptic depends mainly on his own psychic makeup and other factors yet unknown; focal occlusions of smaller or larger intracranial vessels, with ensuing focal parenchymal lesions, may or may not be a contributory factor. As recently emphasized by Moersch [21] in the discussion of Bruetsch's last paper, "it is not known how numerous or how extensive lesions in the brain must be for the production of mental symptoms."

SUMMARY

Lesions of intracranial vessels occur with unexpected frequency in late stages of rheumatic heart disease. The larger and smaller arteries and veins, mainly in the leptomeninges, show a great variety of pathologic features. The principal lesions are: various forms of thrombosis, endarteritic proliferation, alteration of the elastic membranes, and fibrosis of media and adventitia. The histologic picture, as a rule, is sufficiently characteristic to permit differentiation from other vascular diseases that occur in the same location. Parenchymal changes in the brain secondary to the vascular processes are identical with those produced by other vascular diseases. Focal neurologic signs may occur, but there is little evidence to show that the lesions described form the anatomic basis for psychotic syndromes.

19. Karsner, H. T.: Acute Inflammations of Arteries, Springfield, Ill., Charles C Thomas, Publisher, 1947.

20. Gross, L.; Kugel, M. A., and Epstein, E. Z.: Am. J. Path. **11**:253, 1935.

21. Moersch, F. P.: J. A. M. A. **134**:453, 1947.

MYOCARDIAL CHANGES IN POLIOMYELITIS

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THE OCCURRENCE of myocarditis in poliomyelitis was recognized in 1941, although clinical evidence of myocarditis and of cardiac irregularity had been reported prior to that date by two observers. Hertz, Johnson and Depree,[1] in 1913, reported a case of myocarditis of several months' duration, with recovery. Neal,[2] in 1932, mentioned briefly several fatal cases with rapid pulse, and with cyanosis persisting despite the use of the respirator, and 1 case with intervals of great cardiac irregularity; in these cases death was attributed to the involvement of cerebral vital centers.

The first report on microscopic evidence of myocarditis in poliomyelitis was that of Larson,[3] in 1941, who encountered myocarditis in 2 of 12 necropsies of that disease. These cases were described in detail two years later by Dublin and Larson.[4] In 1942, before the appearance of the latter paper, Saphir and Wile[5] reported that myocarditis had been observed in 6 of 7 necropsies of infantile paralysis. In the following year three papers appeared: the detailed report of Dublin and Larson[4]; a paper by Peale and Lucchesi,[6] who reported acute myocarditis observed in 5 of 9 cases of poliomyelitis, and Hassin's[7] report of a case. In a more recent article Saphir[8] encountered myocarditis in 10 of 17 necropsies of poliomyelitis.

From the Pathologic Laboratories, Willard Parker Hospital.

1. Hertz, A. F.; Johnson, W., and Depree, H. T.: Guy's Hosp. Rep. **67**:105, 1913.

2. Neal, J. B., in Poliomyelitis: International Committee for the Study of Infantile Paralysis, Baltimore, Williams & Wilkins Company, 1932, pp. 175 and 176.

3. Larson, C. P.: Northwest Med. **40**:448, 1941.

4. Dublin, W. B., and Larson, C. P.: Am. J. Clin. Path. **13**:15, 1943.

5. Saphir, O., and Wile, S. A.: Am. J. M. Sc. **203**:781, 1942.

6. Peale, A. R., and Lucchesi, P. F.: Am. J. Dis. Child. **65**:733, 1943.

7. Hassin, G.: J. Neuropath. & Exper. Neurol. **2**:293, 1943.

8. Saphir, O.: Am. J. Path. **21**:99, 1945.

In an earlier description of myocarditis in a case of infantile paralysis, in 1937, Clark,[9] attributed the cardiac lesions to serum disease and serum carditis following administration of horse serum.

Electrocardiographic studies of patients with poliomyelitis also showed evidence of cardiac damage in that disease. Battro, Cibils Aguirre and Mendy,[10] in Argentina, found transient myocarditis in 4 of 20 patients in the acute stage of poliomyelitis, and none in 18 in the chronic stage. Morrow [11] has observed abnormal electrocardiographic tracings of some convalescent patients in the Poliomyelitis Division of the Knickerbocker Hospital in New York.

All pathologic reports showed a high incidence of acute myocarditis in fatal cases of infantile paralysis. However, each report was based on a small number of cases which did not permit a fair estimation of the actual incidence of this complication.

The present report was undertaken for the purpose of establishing the incidence of acute myocarditis in poliomyelitis in the large pathologic material of the Willard Parker Hospital. The material available in the files, covering the years from 1929 to 1947 inclusive, exceeded by far the combined number of cases reported to date in the literature. Sections of the myocardium were available from the majority of the old, and from all the more recent, complete necropsies, and acute myocarditis had been recorded as the cause of death in several cases.

MATERIAL

The present report is based on microscopic study of the material from 92 patients with poliomyelitis. All but 1 were in the acute or the convalescent stage of the disease; 1 patient, ill for ten months, was considered as having a chronic involvement.

Sections from the myocardium were searched for lesions of acute myocarditis; the lungs were examined for pulmonary changes, and the pathologic and clinical observations were correlated. Only cases with acute focal myocardial lesions were considered as positive for the complication in question. Cases of rheumatic heart disease were recorded as negative.

Acute focal myocarditis was found in 16 of 92 cases of poliomyelitis examined. The duration of poliomyelitis in the cases with myocardial lesions was from two to ten days, and in the majority of them (12 cases) did not exceed five days. The age of the patients ranged from 13 months to 37 years. Death from cardiac failure was recorded in 4 cases. In 2 other cases the clinical picture was suggestive of cardiac damage. Two patients had received intravenous injections of antipoliomyelitis horse serum one and three days before death, respectively. In all cases bulbar and spinal involvement of varying severity was observed microscopically, and in several, also involvement of the midbrain and the cortex.

Brief abstracts from 8 clinical histories are presented.

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9. Clark, E.: J. A. M. A. **110**:1098, 1938.

10. Battro, A.; Cibils Aguirre, R., and Mendy, J. C.: An. d. Inst. de invest. fisiol. **5**:7, 1943.

11. Morrow, D. J.: Personal communication to the authors.

CASES OF POLIOMYELITIS WITH CLINICAL EVIDENCE OF CARDIAC FAILURE

CASE 1.—A white boy 13 months old was admitted on the second day of an illness characterized by malaise, a temperature of 101.6 F. and paralysis of one leg only. The spinal fluid contained 230 cells. On the fourth day of illness he became cyanotic and apparently died of heart failure. Necropsy note: no pneumonia.

CASE 2.—A white girl 3½ years old was admitted on the third day of an illness characterized by headache, stiff neck, fever, vomiting and weakness of the muscles of the left leg. The spinal fluid contained 560 cells. On the fifth day of illness she died apparently of cardiac failure. Necropsy note: no pneumonia.

CASE 3.—A white boy 14 years old was admitted on the third day of an illness characterized by fever (temperature 103.2 F.) headache, pain in the neck, vomiting, inability to swallow, nasal voice and palsy of the right side of the face. The extremities were intact. The spinal fluid contained 310 cells. On the fourth day of illness the temperature was 105.6 F., the pulse was rapid, the heart sounds were of poor quality and a systolic murmur was heard over the precordium; the patient died a few hours later. Necropsy note: no pneumonia.

CASE 4.—A Negro boy 6 years old was admitted on the third day of illness. He had a headache, pain in the back of his neck, paralysis of the left side of the face and a temperature of 104.4 F. The spinal fluid contained 330 cells. On the fourth day he was unable to swallow. On the fifth day the pulse became irregular. This continued for three days. On the eighth day of illness the patient died of cardiac failure, with the heart stopping before the respirations ceased. Necropsy note: hypostatic pneumonia.

CASE 5.—A white boy 8½ years old was admitted with a history of headache and fever for the past six days and of nasal voice since the preceding day. On admission there was difficulty in swallowing and a temperature of 104 F. The spinal fluid contained 85 cells. The pulse rate changed intermittently from 110 to 140. On the seventh day of illness the patient was semicomatose. He died on the tenth day of illness. Necropsy note: pneumonia in a few alveoli in one section only.

CASE 6.—A white girl 11 years old was admitted on the fourth day of an illness which was characterized by vomiting followed by inability to sit up or turn her head. On admission she had nasal speech, weakness of the left side of the face and palate and bilateral weakness of the sternocleidomastoid muscle. Her mouth was full of blood-tinged mucus and froth. Her temperature was 101 F.; the pulse rate was 110 to 120; the blood pressure, 146 systolic and 100 diastolic. On the fifth day she suddenly ceased to breathe. Necropsy note: hemorrhagic infarct in one lung; mucus in bronchi, but no bronchitis or pneumonia.

CASES IN WHICH PATIENTS WERE TREATED WITH IMMUNE HORSE SERUM

CASE 7.—A white boy 14 years old was admitted on the second day of an illness characterized by pain in the back and the neck, vomiting, and weakness of the left arm. The temperature was 103 F. The spinal fluid contained 310 cells. He received on admission 10 cc. of immune horse serum intravenously. Shortly thereafter, a headache and chill developed and the temperature rose to 104.4 F. On the following day the paticnt had involvement of intercostal muscles and was placed in the respirator, but he became cyanotic and unconscious and died a few hours later, on the third day of illness and one day after the administration of the horse serum. Necropsy note: no pneumonia.

CASE 8.—A white girl 8 years old was admitted on the second day of illness with pain in the back, headache, rigidity of the neck and a temperature of 102.6 F. The spinal fluid contained 130 cells. The diagnosis was preparalytic poliomyelitis, and 10 cc. of immune horse serum was given intravenously. Two days later, there was weakness of the right leg, and another 10 cc. of immune horse serum was given intravenously. One and one-half hours later the patient had a flushed face, was dyspneic and showed some involvement of intercostal muscles. On the next day, the fifth day of the disease, and three days after the first dose of horse serum, she died, apparently from respiratory paralysis. Necropsy note: no pneumonia.

Of the remaining 8 patients, 1 died of pneumonia and the rest with manifestations of either bulbar or respiratory paralysis.

PATHOLOGIC CHANGES IN THE MYOCARDIUM

Focal Myocarditis.—Three types of focal myocardial lesion were observed.

The first type of lesion was the least conspicuous. At low magnification it appeared as areas containing a greater number of nuclei than the rest of the myocardium (fig. 1 *A*). At high magnification one could see in those areas isolated thin and cloudy myocardial fibers, tapering off toward the widened, edematous stroma, and long, wavy nuclei clinging to the fibers (fig. 1 *B*). No cytoplasm could be distinguished around those nuclei, which apparently did not belong to cells of hematogenous origin. In some cases the cells seemed to originate from the endothelium of the capillaries, while in others they appeared to derive from the interstitial stroma of the myocardium. This lesion was seen best in longitudinal sections of the muscle fibers. This type of lesion was noted in 5 cases.

The second type of lesion consisted of cellular collections between intact or only slightly degenerated myocardial fibers. The infiltrating cells usually were mononuclear, with only occasional polymorphonuclear ones. In some foci the mononuclear cells were all lymphocytes (fig. 1 *C*). In others the mononuclear cells had elongated or oval nuclei and little cytoplasm and seemed to be of histiocytic origin (fig. 1 *D*). The character of infiltrates in a given block of tissue was fairly constant, but in lesions located in distant parts of the same heart the character of cells was often variable. In 1 case, for instance, the infiltrates in the wall of the left ventricle consisted of elongated histiocytes, while in the wall of the left auricle all infiltrating cells were lymphocytes. This type of lesion was seen in 8 cases.

The third type of lesion consisted of cellular collections in the interstitial tissue surrounding the blood vessels and was encountered as an independent lesion or in combination with the preceding types. The cells usually were histiocytic mononuclears with oval nuclei (fig. 2),

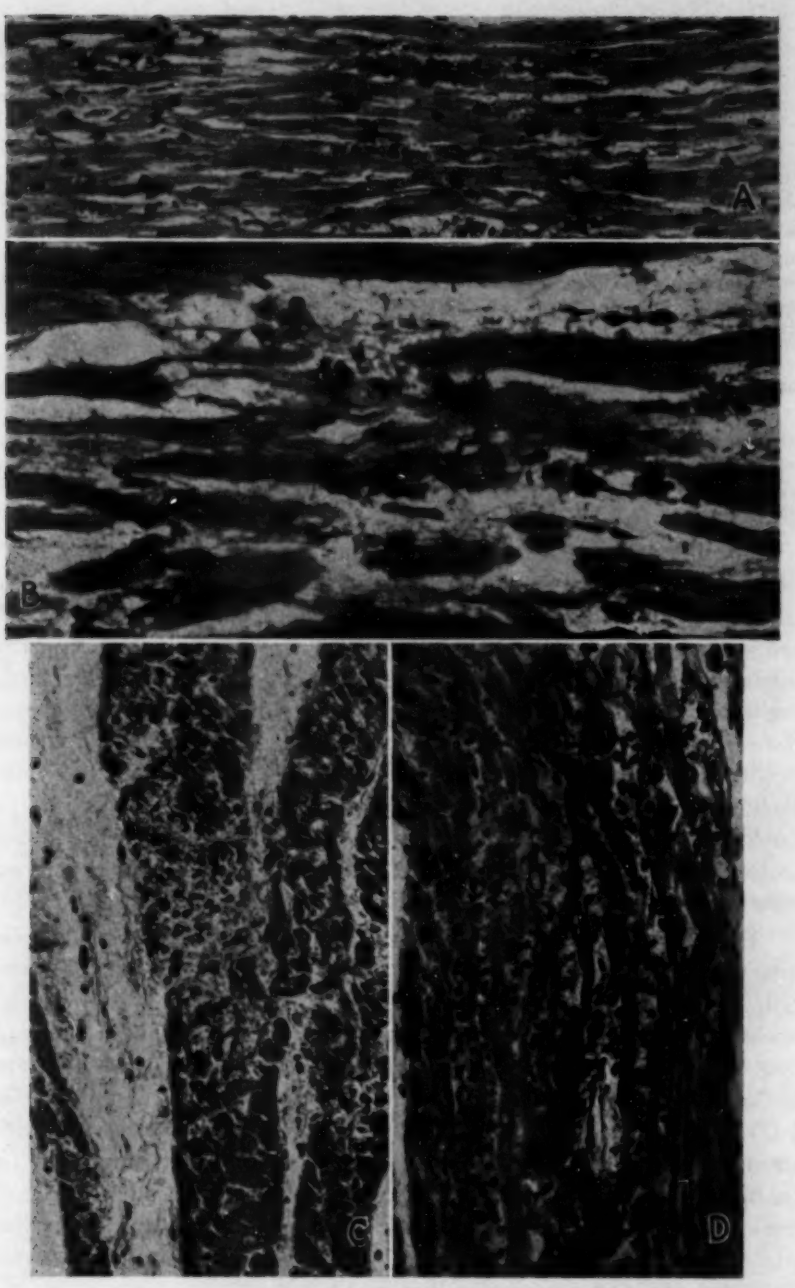

Fig. 1.—*A*, mononuclear cells clinging to individual myocardial fibers in case 5 (× 220).

B, similar lesion from another case under higher magnification (× 440). Note the elongated and wavy nuclei at the borders of degenerated, thin, tapering myocardial fibers.

C, lymphocytic collections in myocardial bundles; interstitial edema in case 1 (× 220).

D, collections of mononuclear cells with oval nuclei, and some lymphocytes, between slightly damaged myocardial fibers in case 4 (× 220).

but in 2 cases polymorphonuclears and lymphocytes predominated in the perivascular tissue and infiltrated between the adjacent muscle fibers (fig. 3*A*).

In several cases small collections of lymphocytes and polymorphonuclears were observed beneath the endocardium, sometimes spreading between the underlying myocardial fibers. Subepicardial cellular collections were frequent, especially in the cases with epicardial petechiae. Petechiae were also frequent within the myocardium and beneath the endocardium.

Fig. 2.—Interstitial perivascular collections of histiocytic cells in case 2 (× 440).

The individual inflammatory foci were small, and several foci were found in one section. However, foci of myocarditis were only rarely encountered in more than two blocks of tissue from the same heart, a fact indicating that the process was not diffuse. The lesions were most frequently located in the posterior wall of the left ventricle and in the posterior papillary muscle, but occasional small foci were encountered in the wall of the left auricle and in the interventricular septum.

There was no relation between the number and severity of focal myocardial lesions and the duration of poliomyelitis or the presence of inflammatory changes in the lungs. The majority of patients with myocarditis died within the first five days of illness. The length of illness

and the pulmonary pathologic conditions in the 16 cases of myocarditis are listed in tables 1 and 2.

Pneumonia was observed in 4 cases, but in 2 it presented the characteristics of hypostatic pneumonia and could perhaps be regarded as a sequel rather than the cause of myocarditis. In 4 cases there were only minimal inflammatory changes in the lungs, and in the case of the hemorrhagic infarct, again, the lesion was to all evidence the result of myocarditis. No inflammatory changes were found in the lungs of 8 patients with myocarditis.

Interstitial Edema.—Interstitial edema of the myocardium was present in all but 6 of the 92 hearts examined. In many cases it not

TABLE 1.—*Length of Illness*

Days	Cases
2	1
3	2
4	4
5	5
6	2
8	1
10	1
Total	16

TABLE 2.—*Pathologic Changes in the Lungs*

	Cases
Lobular pneumonia	2
Hypostatic pneumonia	2
Peribronchitis	2
Pneumonia in a few alveoli in one section only	1
Hemorrhagic infarct with some polymorphonuclear invasion	1
No inflammatory changes in the lungs	8
Total	16

only involved the perivascular connective tissue but extended within the muscle bundles, between individual myocardial fibers.

Degenerative Changes in the Myocardium.—Isolated thin and cloudy myocardial fibers, with mononuclear cells clinging to them, were present in the first type of focal myocarditis presented here, constituting the main feature of that lesion. However, in the majority of cases of myocarditis the heart muscle was remarkably well preserved. Zenker's type of degeneration was encountered occasionally in isolated fibers in several specimens, usually in cases without focal myocarditis. A peculiar widespread degenerative change was observed in some cases with or without myocarditis. The degenerated fibers, when casually examined, appeared to be hydropic because of empty spaces within the sarcolemma. On closer examination, however, it became evident that the lesion consisted of intrasarcolemmal fragmentation of the fibrillae.

The fibrillae, still preserving their cross striation, appeared to be cleaved across the intercalated disks and retracted on either side of the tear while the intact sarcolemmal sheath over the gap became partly collapsed after the recession of the contractile components of the myocardial fiber (fig. 3 *B*). This fragmentation differed significantly from intrasarcolemmal fragmentation of the myocardium observed in the early, degenerative phase of diphtheritic myocarditis, because in the latter disease the fragmented muscle shows Zenker's degeneration with swelling and fusion of the fibrillae and complete obliteration of their striation.

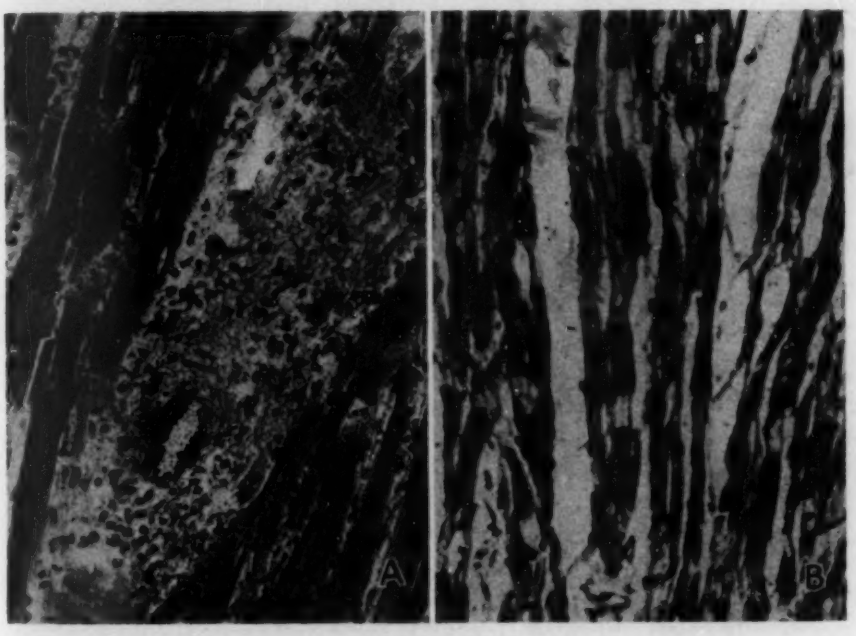

Fig. 3.—*A*, interstitial collections of polymorphonuclears, with some infiltration between intact myocardial fibers in case 7 (× 220). The artery is intact.
B, intrasarcolemmal fragmentation of myocardial fibers in a case in which there was no myocarditis (× 220). The striation of the myofibrillae is largely preserved.

COMMENT

Of all lesions mentioned in the foregoing section, myocarditis is undoubtedly the most important. Focal myocarditis has been seen in other virus diseases—for example, in mumps (Manca [12]), in infectious mononucleosis (Allen and Kellner [13]), which presumably is a virus disease, and in influenza A infection (Finland and associates [14]). Myo-

12. Manca, C.: Arch. ital. di anat. **3**:707, 1932.
13. Allen, F. H., and Kellner, A.: Am. J. Path. **23**:463, 1947.
14. Finland, M.; Parker, F., Jr.; Barnes, M. W., and Jolliffe, L. S.: Am. J. M. Sc. **209**:455, 1945.

carditis of a virus origin has been produced experimentally in animals (Schmidt [15]).

The etiologic relation of myocardial lesions and the virus of poliomyelitis cannot, obviously, be established on the basis of purely morphologic study and would require experimental corroboration. However, the analysis of our cases points to the possibility of such a relation. The only bacterial inflammatory process that could be expected to occur within the short duration of the poliomyelitis in our cases complicated by myocarditis (two to ten days) would be pneumonia and bronchitis. Stone [16] observed focal myocardial infiltrates in 13.5 per cent of cases of bronchopneumonia. However, bronchopneumonia was present in only 2 of our 16 cases, and bronchitis with peribronchial and minimal interstitial infiltration in 2 cases; the hypostatic pneumonia in 2 other cases could very well have been secondary to the myocarditis. In 8 cases no inflammatory process was found in the lungs or the bronchi, and in 2 the inflammatory changes were limited to a small portion of one microscopic field and were negligible in extent. The etiologic factor in these 10 cases was, therefore, probably nonbacterial. Moreover, the occurrence of myocarditis on the second and third day of poliomyelitis in 3 of our cases and the death of cardiac failure on the fourth and fifth day of illness in 3 other cases indicate that myocarditis may be a very early complication developing before bacterial invasion of the respiratory organs becomes sufficiently severe to lead, in turn, to focal myocarditis.

The 2 cases in which focal myocarditis occurred in patients treated with immune horse serum require a special discussion. Interstitial myocardial infiltrates and vasculitis in patients with serum disease following the administration of horse serum had been described by Clark and Kaplan [17] and the possibility of a similar reaction in our cases had therefore to be considered. However, in our cases myocarditis developed too soon after the administration of the serum to be the result of an allergic reaction, as the patients died one and three days, respectively, after the treatment, before serum disease could develop. The morphologic aspect of the myocardial lesions was also different from that of the lesions observed by Clark and Kaplan. No vasculitis was seen in either case. The interstitial cellular infiltrates in one case consisted predominantly of polymorphonuclears, while in the other case collections of lymphocytes were present between intact myocardial fibers. In the instances of serum carditis the predominant cells of perivascular infiltrates were histiocytes and fibroblasts. Neither of our patients had

15. Schmidt, E. C. H.: Am. J. Path. **24**:97, 1948.
16. Stone, W. J.: Am. J. M. Sc. **163**:659, 1922
17. Clark, E., and Kaplan, B. I.: Arch. Path. **24**:458, 1937.

pneumonia. The cause of myocarditis in these cases was, therefore, probably not different from that in other cases.

From the point of view of morphology the focal myocardial lesion in poliomyelitis is not uniform. The lesions of the first type described here are similar to those observed by Finland and associates in influenza A virus infection. Lesions of the second and the third type, with some modification of cellular components and degree of intensity, not only are encountered in a variety of bacterial and rickettsial diseases but have been seen in mumps and infectious mononucleosis. The myocarditis in infantile paralysis is of less extent than that in scarlet fever, diphtheria or rickettsial diseases. The damage to the muscle fibers in the foci of myocarditis in poliomyelitis is, as a whole, relatively small, especially as compared with that in diphtheria, in which severe Zenker's degeneration precedes the inflammatory infiltration.

The incidence of myocarditis in our material, observed in 16 of 92 cases, or 17.4 per cent, is lower than that recorded by other observers. However, it must be taken into consideration that in our material, largely taken from the files, few sections were available from individual specimens. In slightly over one half of our material, 47 cases, only one section was on hand. Acute focal myocarditis was seen in 5 cases, or in 10.6 per cent of that group. In the remaining 45 cases, with two to eight blocks from each specimen, myocarditis was encountered in 11 cases, or in 26.6 per cent. As mentioned before, the myocarditis was not diffuse, and it is obvious that multiple blocks afforded a better opportunity of finding the widely scattered focal lesions. We feel, therefore, that the latter figure of approximately 27 per cent is probably closer to the actual incidence of focal myocarditis in fatal poliomyelitis than the incidence calculated from our total material. The myocarditis may in some cases be regarded as the immediate cause of death.

SUMMARY

Focal myocarditis was found in 16 of 92 cases of poliomyelitis. The incidence of myocarditis in 45 cases in which multiple sections from each heart were available was 26.6 per cent. Cardiac failure was the immediate cause of death in at least 4 cases.

Three histologic types of lesions are described.

In most of the cases the myocarditis was observed between the second and the fifth day of illness. Pneumonia and other evidence of pulmonary inflammation were absent in one half of the 16 cases.

Myocardial interstitial edema was present in most of the 92 cases.

Intrasarcolemmal fragmentation of myocardial fibers with preservation of striation in the retracted fibers and collapse of the sarcolemmal sheath was seen in many cases in which no myocarditis was found, and in a few cases of myocarditis.

COMPARISON OF THYMIC HYPERPLASIA IN MYASTHENIA GRAVIS AND EXOPHTHALMIC GOITER*

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THE functions of the thymus remain undetermined, and there has been much controversy concerning metabolic disturbances attributed to thymic dysfunction. There is suggestive evidence that the thymus plays an endocrine role. Hyperplasia of the thymus occurs in acromegaly, hypofunction of the adrenal glands (Addison's disease), castration, hyperthyroidism and myasthenia gravis. Simpson and co-workers [1] found that in the rat adrenalectomy caused thymic enlargement, while, conversely, administration of an extract containing the adrenocorticotropic factor of the pituitary gland caused an involutionary change in the thymus and the lymph nodes. Marine, Manley and Baumann [2] found, while working with rabbits, that gonadectomy combined with adrenalectomy was the most powerful stimulus for thymic regeneration, but thyroid secretion was necessary for this change to take place. Pregnancy is known to hasten thymic involution, and Viets, Schwab and Brazier [3] presented a case in which a marked remission of myasthenic symptoms occurred during preghancy.

In recent years, thymectomy has been resorted to with gratifying results in many of the cases of myasthenia gravis. For this reason a histopathologic study was made of the thymus in this disorder. Since thymic hyperplasia occurs also in other endocrine disorders, a compari-

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* Abridgment of a thesis submitted by Dr. Bryan to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery.

1. Simpson, M. E.; Li, C. H.; Reinhart, W. O., and Evans, H. M.: Proc. Soc. Exper. Biol. & Med. **54**:135, 1943.

2. Marine, D.; Manley, O. T., and Baumann, E. J.: J. Exper. Med. **40**:429, 1924.

3. Viets, H. R.; Schwab, R. S., and Brazier, M. B., cited by Wilson, A., and Stoner, H. B.: Quart. J. Med., **13**:1, 1944.

son was made with the thymic hyperplasia of hyperthyroidism. The thymuses of hyperthyroid patients were selected for the comparative study because of the availability of specimens. The cases were limited to those of exophthalmic goiter because it was thought that the pathologic features would be more constant.

Cancers of the thymus were not included, since a report on such tumors was made previously by Murray and one of us.[4] Also, extensive investigation of the complex endocrinologic problems of the thymus is outside the scope of this paper.

REVIEW OF THE LITERATURE

Normally the thymus begins to involute at puberty. The involution probably is due to the initiation of gonadal function. Also at puberty there is involution of the lymph nodes.[5] Hammar[6] showed that from birth until puberty there is an absolute increase in the weight of the thymus, and that after puberty there is involution without complete disappearance. However, Kasarinow[7] stated that there is little if any growth after birth.

Reinhart and Wainman[8] studied the thymus, the lymph nodes and the spleen in male rats after thyroidectomy, castration and replacement therapy and observed that when changes occur in one of these lymphoid tissues they are likely to occur in the others.

In myasthenia gravis, the myoneural junction is affected, and there is manifested an abnormal fatigability of the skeletal muscles with slow progression and remission. The muscles most frequently affected are those supplied by the cranial nerves. It was Weigert[9] who, in 1901, first demonstrated persistence of the thymus in myasthenia gravis. Bell,[10] in 1917, reported that in 27 of 56 cases of myasthenia gravis thymic abnormality occurred. Blalock and co-workers[11] summarized the literature on the thymus in myasthenia gravis up to 1939 when they presented data on 110 patients who had come to operation or autopsy; of 53 of these patients who had some abnormality, 31 had tumors and 22 had enlarged or persistent thymuses.

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4. Murray, N. A., and McDonald, J. R.: Am. J. Clin. Path. **15**:87, 1945.
5. Cowdry, E. V.: Special Cytology: The Form and Functions of the Cell in Health and Disease, ed. 2, New York, Paul B. Hoeber, Inc., 1932, vol. 2, p. 836.
6. Hammar, J. A.: Klin. Wchnschr. **8**:1385, 1929.
7. Kasarinow, G., cited by Bratton, A. B.: J. Path. & Bact. **28**:609, 1925.
8. Reinhart, W. O., and Wainman, P.: Proc. Soc. Exper. Biol. & Med. **49**:257, 1942.
9. Weigert, C., cited by Murray and McDonald.[4]
10. Bell, E. T.: J. Nerv. & Ment. Dis. **45**:130, 1917.
11. Blalock, A.; Mason, M. F.; Morgan, H. J., and Riven, S. S.: Ann. Surg. **110**:544, 1939.

Exophthalmic goiter was shown by Markham,[12] in 1858, to be associated with an enlarged thymus. Other early investigators presented similar reports.[13] Kocher,[14] in 1914, published data on 14 cases of exophthalmic goiter, in 42 per cent of which hyperplasia of the thymus and of other lymphoid organs occurred. Margolis [15] stated that the incidence of thymic hyperplasia in cases of exophthalmic goiter is 85 per cent.

There seems to be a reciprocal effect between the thyroid gland and the thymus, the former stimulating, the latter inhibiting, the production of estrogen and androgen. Gudernatsch [16] found that the thyroid gland stimulates, and the thymus suppresses, growth and differentiation of tissues. In one of McEachern's [17] cases of myasthenia gravis combined with hyperthyroidism there was marked aggravation of myasthenic signs and symptoms several days after thyroidectomy. On the other hand, Kowallis and co-workers [18] reported a case in which the myasthenic and hyperthyroid manifestations disappeared after subtotal thyroidectomy.

EMBRYOLOGIC FEATURES

The thymus is of ectodermal-endodermal origin, the ectoderm of the cervical sinus joining the primitive cortex of the gland by migrating to surround the endodermal thymus which is derived from the third branchial pouch. At the 24 mm. stage there are, according to Norris,[19] three zones: (1) the outer cortical layer of ectoderm, (2) the intermediate lymphocytic layer, which is of mesenchymal origin and which secondarily invades the gland after the entrance of the vessels and connective tissue, and (3) the inner medullary endodermal component. The two types of reticulum cells are (1) the compact epithelial endodermal mass which forms the syncytial cytoreticulum and (2) the ordinary fibrous reticulum of the gland which is derived from the cells of the adventitia of the small blood vessels, the capsule and the interlobular septums.

Hassall's corpuscles are formed from some of the cells which are crowded into the medulla by the subcortical lymphocytes. The early

12. Markham, cited by Kowallis, Haines and Pemberton.[18]

13. MacKenzie, H., and Edmunds, W.: Tr. Path. Soc. London **48**:192, 1897. Soupault, M.: Bull. Soc. anat. de Paris **72**:592, 1897.

14. Kocher, A.: Arch. f. klin. Chir. **105**:924, 1914.

15. Margolis, H. M.: Ann. Int. Med. **4**:1112, 1931.

16. Gudernatsch, cited by Capelle, W.: Deutsche Ztschr. f. Chir. **235**:280, 1932.

17. McEachern, D.: Medicine **22**:1, 1943.

18. Kowallis, G. F.; Haines, S. F., and Pemberton, J. deJ.: Arch. Int. Med. **69**:41, 1942.

19. Norris, E. H.: Contrib. to Embryol. **27**:193, 1938.

Hassall's corpuscles are seen to be made up of a plaquelike arrangement of two to three of these large cells having large ovoid vesicular nuclei.

Thus, the endoderm of the third branchial pouch gives rise to the syncytial cytoreticulum which is apart from the fibrous reticulum, the lymphocytes invade the gland from without and have a mesenchymal origin, and the ectodermal cervical sinus gives rise to the primitive thymic cortex and the corpuscles of Hassall.

HISTOLOGIC CHARACTERISTICS

Maximow and Bloom [20] described the thymus as consisting of two lobes made up of many lobules which have a light-staining medulla surrounded by a darker-staining cortical portion. In the cortex are densely packed masses of small cells which are morphologically identical with the small lymphocyte. These cells average 6 microns in diameter and have a very small amount of cytoplasm, a dark nucleus with heavy chromatin particles, and a distinct nucleolus. Among these are elongated reticular cells with a pale round or oval nucleus, a smooth nuclear membrane, a few small chromatin particles and one or two nucleoli. As the examination proceeds from the cortex to the medulla, one notes that most of the lymphocytes disappear abruptly.

The medulla consists predominantly of reticular cells, which can be seen to form a syncytium, the meshes of which are filled with lymphocytes. Cowdry [21] said that the reticular cell of the thymus looked to him exactly like the reticular cell of the lymph nodes and the spleen. The medulla also contains Hassall's corpuscles, which are acidophilic, rounded structures 30 to 100 microns in diameter composed of concentrically arranged cells, many of which show evidence of degeneration and hyalinization. Reticular cells are connected at one or more places at the periphery of Hassall's corpuscles.

PATHOLOGIC FEATURES

Myasthenia Gravis.—There are no constant pathologic changes in the thymuses of patients with myasthenia gravis; when thymoma is excluded, there remain only normal glands or those which have become hyperplastic. The "persistent" glands are considered to be those glands of older age groups which have not atrophied and which have not been replaced by fat. These same persistent glands should be considered normal, since there is a great variance in the preservation of the normal appearance of the thymus, and they are not hyperplastic nor are they cancerous. We therefore have referred to all the thymuses which are

20. Maximow, A. A., and Bloom, W.: A Textbook of Histology, ed. 4, Philadelphia, W. B. Saunders Company, 1942, p. 324.

21. Cowdry, E. V.: A Textbook of Histology: Functional Significance of Cells and Intercellular Substances, ed. 2, Philadelphia, Lea & Febiger, 1938, p. 162.

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not cancerous or hyperplastic as normal glands whether much or little of the glandular tissue remained.

There are two types of hyperplasia of the thymus: that of the epithelial syncytium and that of the lymphocytic tissue. Norris [22] stated that in myasthenia gravis all pathologic changes of the thymus, cancer excluded, represent a varying degree of epithelial hyperplasia, the benign tumor being interpreted as representing extreme epithelial hyperplasia. Homburger [23] found extreme epithelial metaplasia in 2 cases of myasthenia gravis and moderate epithelial metaplasia in 3 cases of thyrotoxicosis and 2 cases of incidentally observed persistence of the thymus in more than 6,000 autopsies. Hoxie [24] spoke of the predominance of epithelial elements in myasthenia gravis. Bell [10] and Miller [25] also stated that in myasthenia the epithelial elements predominate. Likewise, Hardymon and Bradshaw [26] reported epithelial hyperplasia in a case of myasthenia gravis.

Sloan,[27] however, in reexamining Miller's slides, found no hyperplasia of the epithelium but did find definite lymph follicles. Sloan examined the thymuses of 150 people who died suddenly without previous chronic disease, in 14 of which he found lymph follicles with germinal centers; however, when the follicles occurred in normal glands they were few. He found occasional lymph follicles in most normal thymus glands when serial sections were examined. Blalock [28] reported 10 cases of lymphoid hyperplasia with germinal center formation, in one of which the hyperplasia was impressive, in a series of 20 cases in which thymectomy had been performed for myasthenia. Also, there were 2 cases of tumor in this group. Giordano and Haymond [29] found diffusely scattered homogeneous lymphocytes in a reticulum cell stroma.

Norris [19] considered lymphorrhages of skeletal muscle pathognomonic of myasthenia, but Giordano and Haymond found lymphorrhages in only two thirds of their cases, and Dudgeon and Urquhart [30] found lymphorrhages in 8 of 9 cases of exophthalmic goiter and also in cases of myositis.

Hyperthyroidism.—As Margolis pointed out in his work on thymic hyperplasia in hyperthyroidism, there are relatively few reports of a careful histologic study of the thymus. If the weight of the thymus

22. Norris, E. H.: Am. J. Cancer **27**:421, 1936.
23. Homburger, F.: Arch. Path. **36**:371, 1943.
24. Hoxie, G. H.: J. Missouri M. A. **14**:389, 1917.
25. Miller, H. G.: Arch. Path. **29**:212, 1940.
26. Hardymon, P. B., and Bradshaw, H. H.: Surg., Gynec. & Obst. **78**:402, 1944.
27. Sloan, H. E.: Surgery **13**:154, 1943.
28. Blalock, A.: J. Thoracic Surg. **3**:316, 1944.
29. Giordano, A. S., and Haymond, J. L.: Am. J. Clin. Path. **14**:253, 1944.
30. Dudgeon, L. S., and Urquhart, A. L.: Brain **49**:182, 1926.

exceeded the normal, the gland was designated as hyperplastic. Abnormal weight, however, cannot be used as the criteria of hyperplasia. Regrettably, Margolis did not distinguish between lymphoid and epithelial hyperplasia in his series. He reported that there was an 85 per cent incidence of thymic hyperplasia in his cases of exophthalmic goiter.

In 6,000 autopsies Homburger found 3 instances of thyrotoxicosis in which moderate epithelial hyperplasia of the thymus, with numerous young and hyalinized Hassall's corpuscles, had occurred. In 2 cases the separation of cortex and medulla was distinct. In 2 cases the interstitial tissue was fibrous-adipose, while in the third it was adipose.

THE PRESENT STUDY: MATERIALS AND METHODS

All the definitely proved cases of myasthenia gravis in which autopsy or thymectomy had been performed at the Mayo Clinic, with the exception of the cases of thymoma, were included in this study. Dr. L. M. Eaton, of the department of neurology and psychiatry, selected the cases of myasthenia gravis, in all of which, he thought, on the basis of clinical findings and the results of therapeutic trials of prostigmine, the criteria of the disease were fulfilled. When the tissue had been examined histologically and thymoma had been ruled out, 23 cases remained.

For purposes of comparison, a study was made of 20 cases of exophthalmic goiter, taken at random, in which a diagnosis of parenchymatous hypertrophy had been made on the surgical specimen removed at thyroidectomy and in which the patient had died within a brief period after operation and had come to autopsy.

The data on the weight, the size and the gross appearance of the specimen used were taken from the pathologist's report, from the autopsy protocols, from the surgical records or from a combination of these. This was done to obtain a much more accurate and precise description than could be obtained by examination of the fixed specimens alone. In many cases such data were unavailable. Also, slides of the spleen and of lymph nodes, when available, were included in this study. Hematoxylin and eosin stains were used routinely except in 1 instance in which sudan III was used.

It is most essential, in the consideration of this subject, to realize what the term "hyperplasia" implies. According to MacCallum,[31] hyperplasia of an organ is the result of an increase of the number of its cells, whereas hypertrophy is the result of an increase in the size of its elements. Not infrequently, both processes are in evidence. In essential agreement with these definitions are those of Smith and Gault,[32] Boyd,[33] Duval and Schattenberg[34] and Wood.[35]

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31. MacCallum, W. G.: A Textbook of Pathology, ed. 7, Philadelphia, W. B. Saunders Company, 1940, p. 76.

32. Smith, L. W., and Gault, E. S.: Essentials of Pathology, New York, D. Appleton-Century Company, Inc., 1938, p. 35.

33. Boyd, Wm.: Textbook of Pathology, ed. 4, Philadelphia, Lea & Febiger, 1943, p. 254.

34. Duval, C. W., and Schattenberg, H. J.: Textbook of Pathology: A Correlation of Clinical Observations and Pathological Findings, ed. 1, New York, D. Appleton-Century Company, Inc., 1939, p. 98.

35. Wood, F. C.: Textbook of Pathology, ed. 16, Baltimore, William Wood & Company, 1936, p. 77.

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Therefore, in order to interpret the microscopic observations properly, it was necessary to go over many slides of thymuses, including fetal thymuses, normal thymuses of different age groups (fig. 1) and also thymomas. Even after this had been done, the interpretation of the observations was often difficult.

In all cases the criterion which had to be met to allow a possible diagnosis of hyperplasia was an increase in the density or the number of the essential elements of the gland. Many of the specimens examined showed an increase in the density or the number of the essential elements, but the content of thymic tissue in the different sections was often only 5 or 10 per cent; obviously, with thymic cells constituting such a small percentage, there was no hyperplasia. The density of cells

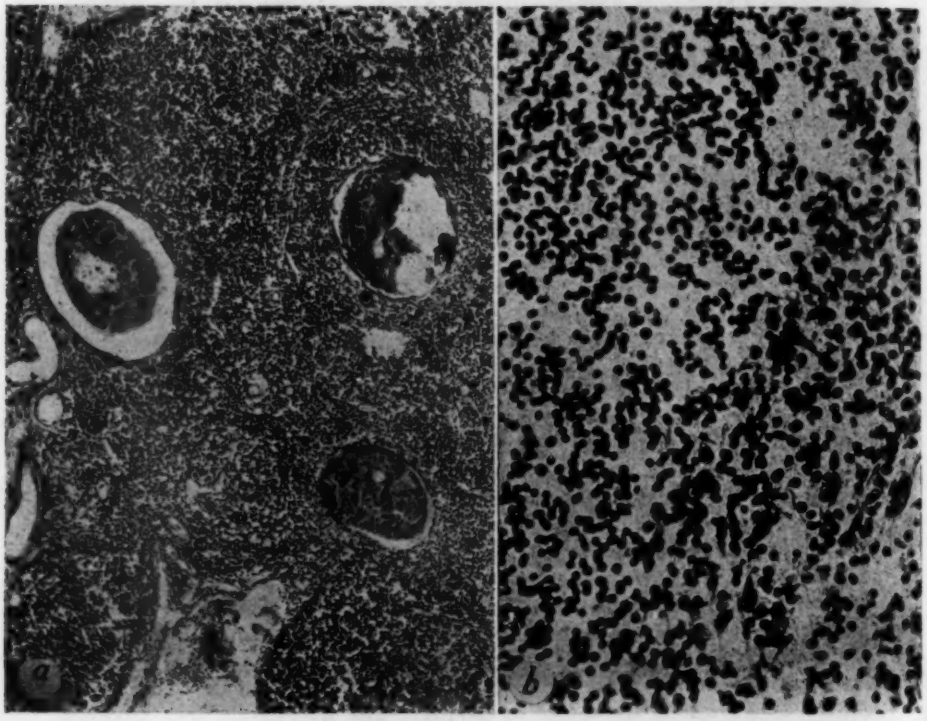

Fig. 1.—Normal thymus: (*a*) × 60; (*b*) × 330.

varied from that of no increase over the normal to that of a marked increase. Associated with the marked increase in density were other indications of potential, if not actual, activity, including the presence of active, proliferative germinal centers.

An attempt was made to grade the extent of hyperplasia of any given section as seen under the microscope. Originally, the classification was based on three grades: minimal, moderate and marked hyperplasia; this, however, was soon found to be too fine a differentiation. Therefore, we patterned our nomenclature after that of Norris[19] and classified the hyperplasia microscopically as moderate and extreme. Hyperplasia was considered moderate when the density of essential thymic elements noticeably exceeded normal, and it was considered extreme when

there was a striking increase over normal. However, the hyperplastic thymic glands in this series showed lymphocytic hyperplasia, whereas those in Norris' series showed hyperplasia of the epithelial elements. In only the myasthenia group were there active germinal centers, and these appeared to be overactive in the cases of extreme hyperplasia. Also, the type of hyperplasia, whether lymphoid or epithelial, was noted.

Another factor, as previously mentioned, is the amount of the gland which is actually thymic tissue, the connective tissue elements, such as fibrous and adipose tissue, being excluded. In this study the percentage of thymic tissue was estimated in regard to the whole gland after a study of several sections of the gland had been made. It was observed that in the glands in which hyperplasia was obvious the percentage of thymic tissue was always at least 70. Therefore, we arbitrarily assumed that in the adult age group a gland, to fulfil another criterion for hyperplasia, should be composed in at least 70 per cent of essential thymic elements.

The age of the patient was another factor that entered into the interpretation, because it is well known that the appearance of the gland in a child is not like that in the older age groups. A normal thymus of a child shows, histologically, a greater percentage of essential thymic elements and increased density. Therefore, in the younger age groups a gland, to be classified as hyperplastic, had to have a correspondingly greater percentage of essential thymic elements than the 70 per cent minimum established for adults.

The glands whose sections did not fulfil the foregoing criteria were then designated as normal glands or thymic fat; the latter designation was used when the thymic tissue was so minimal in the connective tissue that identification of it was next to impossible. The thymus was labeled "normal" when the lobules were distinct, when identification of tissue could be made with ease and when there was no increase in the number of essential thymic elements or when the percentage of thymic tissue was too low for the gland to be considered as hyperplastic.

It may be possible to designate some of these tissues as hyperplastic on the basis of microscopic appearance alone; however, if this is done, one important procedure has been omitted, namely, the determination of gross hyperplasia based on the weight of the gland and the percentage of thymic tissue. Hammar [6] published data on the weights of thymuses of all age groups. Furthermore, he estimated the relative proportions of parenchymatous and interstitial tissues by a more reliable method than that of microscopic estimation. This method consists in tracing the outlines of these tissues in magnified sections and measuring the respective areas with the planimeter. We have taken these values as the standard for comparison; also, we have used Hammar's values for the weight of the thymus. The weights at different ages varied somewhat from series to series, but there was no significant difference between the sexes; therefore, the weights used were the combined averages for the two sexes.

Young and Turnbull [36] stated that their microscopic estimates of the proportions of glandular and interstitial tissues and those of Bratton [37] differ significantly from the values derived by the planimetric method of Hammar,[38] but it seems to us that there is no other practical way to estimate percentages than by simple microscopic study. They also pointed out that naked eye estimation of the ratio of glandular to connective tissue is valueless.

36. Young, M., and Turnbull, H. M.: J. Path. & Bact. **34**:213, 1931.
37. Bratton, A. B., cited by Young and Turnbull.[36]
38. Hammar, J. A., cited by Young and Turnbull.[36]

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Therefore, if we know the weight of the gland and the percentage of the glandular tissue, then by simple multiplication we can determine the weight of the glandular tissue. This value can be compared with normal values, and if it exceeds the upper limit of normal, there is an increase in the number of essential thymic elements, a condition which, by definition, is hyperplasia (table 1). The expected average weight of glandular tissue in a series of normal glands is determined by multiplying the average weight of the glands by the average percentage of glandular tissue. The estimated upper limit of normal is derived, for all practical purposes, by multiplying the average weight of the glands plus twice the standard deviation by the average percentage of glandular tissue. These values have been plotted, and a curve has been drawn which will give the estimated amounts of glandular tissue for the different age groups (fig. 2). If the weight of the gland in question exceeds the estimated upper limit of normal, then for all

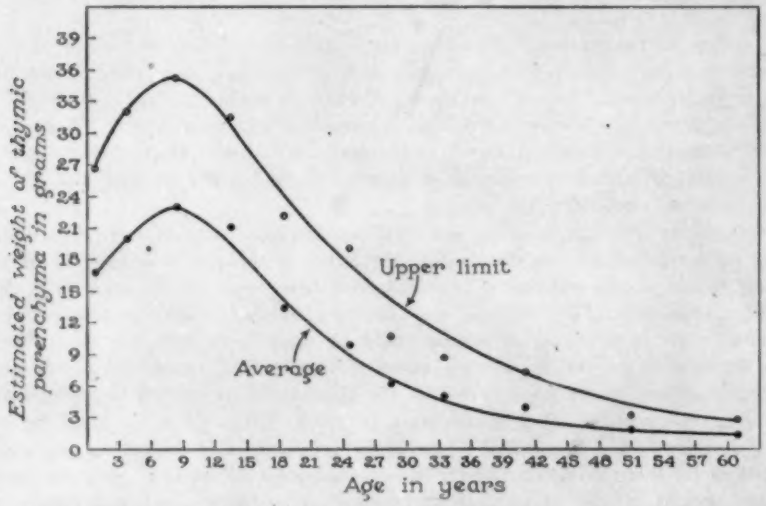

Fig. 2.—Graphically fitted trend lines of estimated average normal and maximal normal weights of thymic parenchyma derived from data in table 1.

TABLE 1.—*Estimated Average Normal and Maximal Normal Weights of Thymic Parenchyma Based on Hammar's Data*

	Thymus				Thymic Parenchyma	
Age, Yr.	Average Weight, Gm.	Standard Deviation, Gm.	Average Weight +2 Times Standard Deviation, Gm.	Thymic Tissue, Average Percentage	Estimated Average Normal Weight, Gm.	Estimated Maximal Normal Weight, Gm.
0-1	20.5	6.1	32.7	81	16.6	26.5
1-6	25.2	8.1	41.4	78	19.7	32.3
6-11	30.4	8.4	47.2	75	22.8	35.4
11-16	29.1	7.0	43.1	73	21.2	31.5
16-21	24.9	8.1	41.1	54	13.4	22.2
21-26	20.3	9.2	38.7	49	9.9	19.0
26-31	18.1	6.5	31.1	34	6.2	10.6
31-36	19.6	7.5	34.6	25	4.9	8.7
36-46	18.9	7.4	33.7	22	4.2	7.4
46-56	16.1	10.8	37.7	11	1.8	4.1
56-66	14.3	7.5	29.3	10	1.4	2.9
66 and over	12.3	5.9	24.1	9	1.0	2.2

practical purposes and by definition hyperplasia has occurred. The peak of the curve representing the upper limit of normal is at 9 years. Table 2, derived from data in figure 2, gives the estimated values for the average normal and the maximal normal weights of thymic parenchyma at stated ages and can be used as a simple guide in determining whether a particular gland is grossly hyperplastic.

FINDINGS

Myasthenia Gravis.—Grossly, the thymic gland was found to be apparently hyperplastic, with the typical butterfly pattern, in 16 of the 23 cases. As to the remaining 7 cases, a small amount of thymic tissue was observed in 1, the thymic tissue had been replaced by fat in 4 and no gross description was available in 2. Microscopically, there was extreme lymphoid hyperplasia in 4 cases (fig. 3) and moderate lymphoid hyperplasia in 2. In the remaining 17 cases the thymus was considered normal or had been replaced by fat. There were no examples of epithelial hyperplasia.

TABLE 2.—*Estimated Average Normal and Maximal Normal Weights of Thymic Parenchyma at Stated Ages as Derived from the Fitted Lines of Figure 2*

Age, Yr.	Estimated Weight of Thymic Parenchyma, Gm.	
	Average Normal	Maximal Normal
1	17.2	27.7
5	21.4	34.0
10	22.4	34.8
15	18.5	29.0
20	13.6	21.9
25	9.1	16.0
30	6.1	11.9
35	4.2	9.3
40	2.9	7.4
45	2.2	5.7
50	2.0	4.4
55	1.8	3.5
Over 55	1.5	2.9

The cytoreticulum of the thymus was arranged, in 15 of the 23 cases, as single cells or groups of two or three cells, while in 4 cases only single cells or occasional small groups of cells were observed. In 2 cases in which the thymus had been replaced by fat, no syncytial cells were found. In 2 cases there was a clustering of the syncytial cells, but only in isolated areas, and in neither instance was it more than might be seen in a normal gland.

The frequency of occurrence and the age of Hassall's corpuscles varied tremendously. In 7 of the 23 cases the Hassall's corpuscles observed were mainly young ones; in the others chiefly hyalinized or calcified corpuscles were present. In 14 of the 23 cases only occasional Hassall's corpuscles were noted, while in 8 cases there was evidence of moderate or frequent occurrence; in 1 case, in which the thymic tissue had been replaced by fat, none were found. The presence of Hassall's corpuscles of a uniform age was not characteristic of any of the types of cases. However, the hyperplastic glands had a tendency to have a larger number of corpuscles.

The interlobular trabeculae were adipose in 15 cases, fibrous in only 2 cases and fibrous-adipose in 6 cases. There was a tendency in the cases of hyperplasia

for only small amounts of interlobular connective tissue to occur, but this tissue, it was observed, could be any one of the three varieties mentioned in the preceding sentence.

Calcium was found in only 5 cases. It usually was seen in Hassall's corpuscles, although it was noted once in the arterioles and once in a gland which had been replaced by fat. Calcium was found in only 1 case of extreme hyperplasia and then only in the corpuscles of Hassall. In all the hyperplastic glands there was distinct lobulation and in 6 normal glands quite definitely outlined lobules. The differentiation of cortex and medulla was clearcut in 2 hyperplastic glands, only fairly well marked in 3 and indistinct in 1. In the 17 normal glands there was

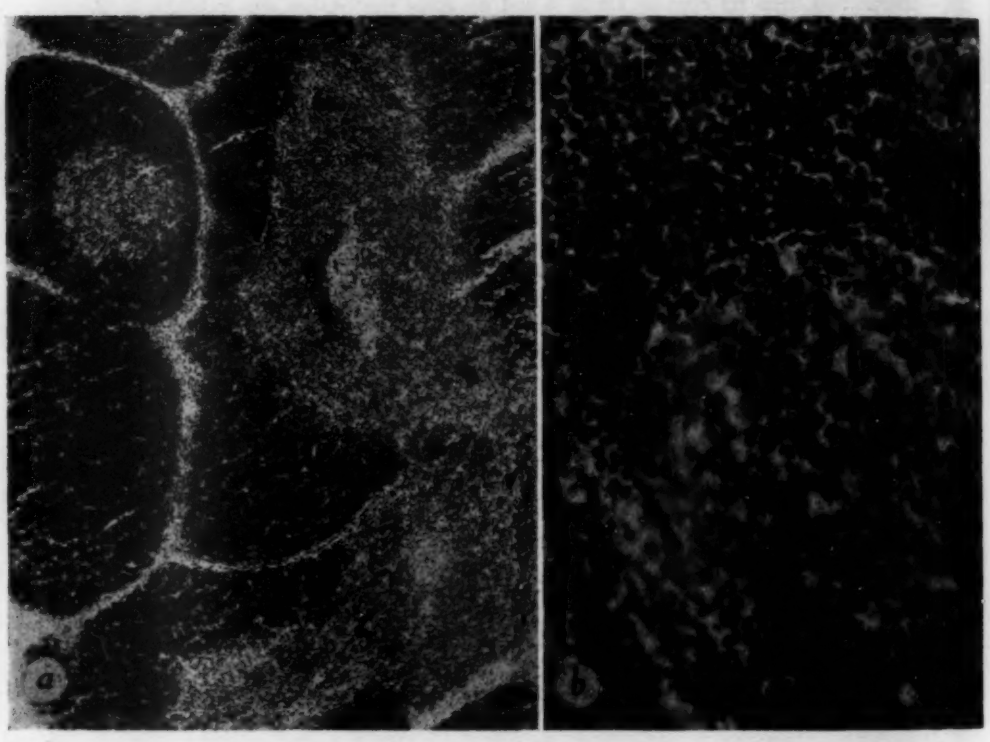

Fig. 3.—Extreme lymphoid hyperplasia of the thymus in myasthenia gravis: (*a*) × 60; (*b*) × 330.

definite differentiation of cortex and medulla in 2, moderate differentiation in 4 and no differentiation in 11.

In the 6 glands of the myasthenia series which were subsequently designated as hyperplastic, the lymphoid tissue was definitely increased over normal, and the areas of extreme hyperplasia were dense and gave an impression of being functionally quite active, with many germinal centers. There were germinal centers along with increased density in the cases of moderate hyperplasia, but this feature was not as characteristic as in the extreme group.

Exophthalmic Goiter.—All the specimens of thymuses in this group were obtained at necropsies. In 8 of the 20 cases of exophthalmic goiter there was no

available gross description. Six of the glands were replaced by fat, and 2 were normal in appearance. In 4 of the 20 cases there was apparent enlargement of the thymus; in one of these the gland exhibited moderate lymphoid hyperplasia microscopically and was described as being large and fleshy and as weighing 39 Gm. (fig. 4). Since this weight was six times the normal expected weight, and since approximately 90 per cent of the tissue was essential thymic tissue, it was evident that this gland was hyperplastic grossly and microscopically. The second of the 4 apparently enlarged glands was described as being enlarged but of normal appearance, with a weight nine times normal, but microscopically this gland was shown

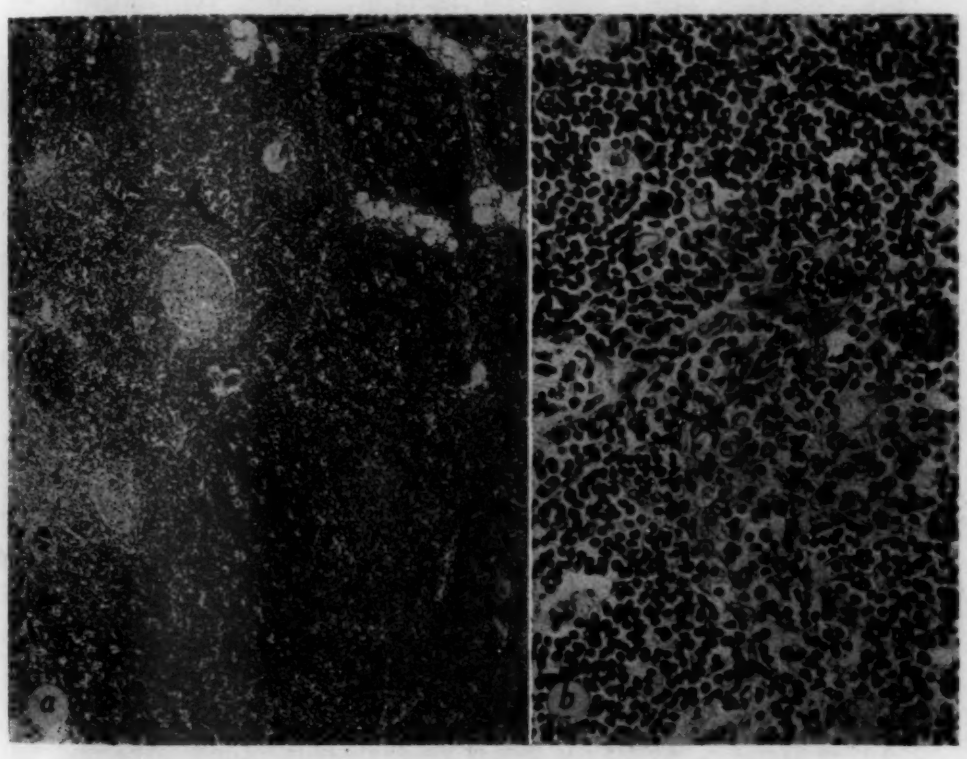

Fig. 4.—Moderate lymphoid hyperplasia of the thymus in exophthalmic goiter: (*a*) × 60; (*b*) × 330.

to be normal. The third apparently enlarged thymus was reported as being markedly "persistent," but the weight was unobtainable, and microscopically this gland, too, appeared to be normal. The fourth apparently enlarged thymus, which was described as being hypertrophied, was an excellent example of the error of designating a gland as hyperplastic on the basis of weight alone. In this case the weight of the thymus of a patient 41 years old was 35 Gm., which is approximately five times the upper limit of normal, but microscopically only 1 or 2 per cent of the gland was composed of essential thymic elements, the remainder being fat. Obviously, this could not have been a hyperplastic gland.

In the exophthalmic goiter series the epithelial syncytium of the thymus did not vary greatly from that in the myasthenia series. In 10 cases the cytoreticulum occurred as single cells or as groups of two or three cells. In 3 cases the syncytial elements ranged from clusters of cells down to single cells. In 4 cases there were next to no epithelial elements, and in 1 case none were seen; in these cases the glandular tissue was minimal, most of the thymic tissue having been replaced by fat.

In only 2 cases were young Hassall's corpuscles in the majority, but in 9 other cases young corpuscles were intermingled with hyaline and calcified corpuscles. In 9 cases hyaline or calcified corpuscles alone occurred. The age of the patient apparently had little to do with the type of corpuscle found, since the average ages of those with and those without young corpuscles were almost exactly the same. The age of the patient had little to do with the age of the corpuscles, since young corpuscles were seen in a normal thymus of a 72 year old man. In 15 glands frequent occurrence of corpuscles was noted, while in 4 Hassall's corpuscles were noted only occasionally, and in 1 there were no corpuscles since the gland was replaced by fat. In 15 of the 20 cases of the exophthalmic goiter series Hassall's corpuscles occurred frequently, the average age of the patients being 48 years; on the other hand, in only 8 of the 23 cases of the myasthenia gravis series did Hassall's corpuscles occur frequently, the average age of the patients being 37 years. The ages ranged from 4 to 72 years in the hyperthyroidism series and from 15 to 74 years in the myasthenia series.

The characteristics of the interlobular trabeculae were almost identical in the exophthalmic goiter series and the myasthenia series, the trabeculae in the former being adipose in 13 instances, fibrous in 2 and fibrous-adipose in 5. Again, in the gland that was hyperplastic there was only a small amount of fibrous-adipose tissue. In the normal thymus of an 11 year old girl there was a small amount of fibrous tissue in the trabeculae.

In 6 cases calcium was found in some of the Hassall's corpuscles, whereas in 14 cases no calcium was found.

There was distinct lobulation of the thymus in 17 of the 20 cases, but in 3 cases in which little thymic tissue was present there was no lobulation but merely a few nests of thymic tissue scattered through the fat. Differentiation of cortex and medulla was fairly definite in only 4 glands, including the single hyperplastic gland, but in the remaining 16 glands there was no differentiation.

In only 1 gland was the lymphoid tissue hyperplastic, and this hyperplasia was only moderate, without germinal centers. In other glands varying amounts of lymphoid tissue were observed, but none had a greater amount than can be seen in a series of normal thymuses. In none of the 20 glands in the hyperthyroidism series were any active germinal centers found.

COMMENT

Thymic Hyperplasia.—In the series of 23 cases of proved myasthenia gravis, exclusive of thymoma, in which thymectomy had been done at the clinic up to April 1946, extreme thymic hyperplasia of the lymphoid type was evident microscopically in 4 cases, moderate lymphoid hyperplasia occurred in 2 and the gland was either normal or consisted of thymic fat in 17. Of the 17 normal glands, 12 showed the density of cells definitely increased as compared with the normal density, and 2 exhibited a few areas in which there was clustering of the epithelial

elements; however, since the average content of thymic tissue in the sections of these 2 glands was only 29 per cent, the glands obviously could not be classified as hyperplastic.

Using the same microscopic criteria as in the myasthenia series, we found no extreme hyperplasia of the thymus in the 20 cases of exophthalmic goiter, and moderate lymphoid hyperplasia in only 1 instance. There was 1 case in which the epithelial elements were increased over the normal, but the other parts of the gland were normal; although 80 per cent of the specimen was thymic tissue, this gland was called normal. Two other glands exhibited a few areas of epithelial clustering, but the percentage of thymic tissue was far below the arbitrary minimum. Five glands showed increased density of cells in the various fields of the slide, but the percentage of thymic tissue was too low to permit considering them as hyperplastic. The average content of thymic tissue in the 8 glands in which density of cells was definitely increased but below the 70 per cent minimum was 38 per cent.

Using Hammar's data, we found, among 13 cases of myasthenia gravis in which the weight of the thymus was available, 2 cases in which the weight exceeded significantly the estimated upper limit of normal, 5 cases in which it exceeded the average weight but was still in the normal range, and 6 cases in which it was less than the average. Comparing the weights obtained by the two methods, we found that, of the glands which showed microscopically extreme hyperplasia, only 1 actually had more thymic tissue than normal, whereas 2 had even less than the average. Of the 2 glands with moderate hyperplasia, the weight of glandular tissue was increased in one, and it was greater than average but within the normal range in the other. In no case did the weight of a gland which was normal microscopically exceed the upper limit of normal.

In the exophthalmic goiter series there were 9 cases in which the weights were available. In 7 of these, significantly excessive amounts of glandular tissue were present, and the glands were, therefore, hyperplastic; however, of these 7 cases, in only 1 was microscopic hyperplasia evident; in the others the gland was normal microscopically.

Other lymphoid organs were also studied to see whether there was any concurrent hyperplasia in the spleen and lymph nodes. In 1 case in the myasthenia series, moderate lymphoid hyperplasia of the lymph node studied was observed, but microscopically the thymus was normal in every respect. In another case, a normal thymus with some increased density of the lymphocytes was noted, whereas the spleen exhibited moderate reticuloendothelial hyperplasia. In another case, in which the thymus showed histologically extreme lymphoid hyperplasia, the lymph node from the trachea showed marked reticuloendothelial hyperplasia,

a condition that is, however, consistent with that seen in anthracosis (fig. 5 *a*). In the exophthalmic goiter series there was no associated hyperplasia of the spleen or lymph nodes, except that one lymph node from the lung showed reticuloendothelial hyperplasia due to anthracosis. Thus it may be seen that there was no correlation between hyperplasia of the thymus and hyperplasia of the lymphoid organs in either of these two series. Young and Turnbull showed that there is considerable variability of volumes of lymphoid structures in the different age groups

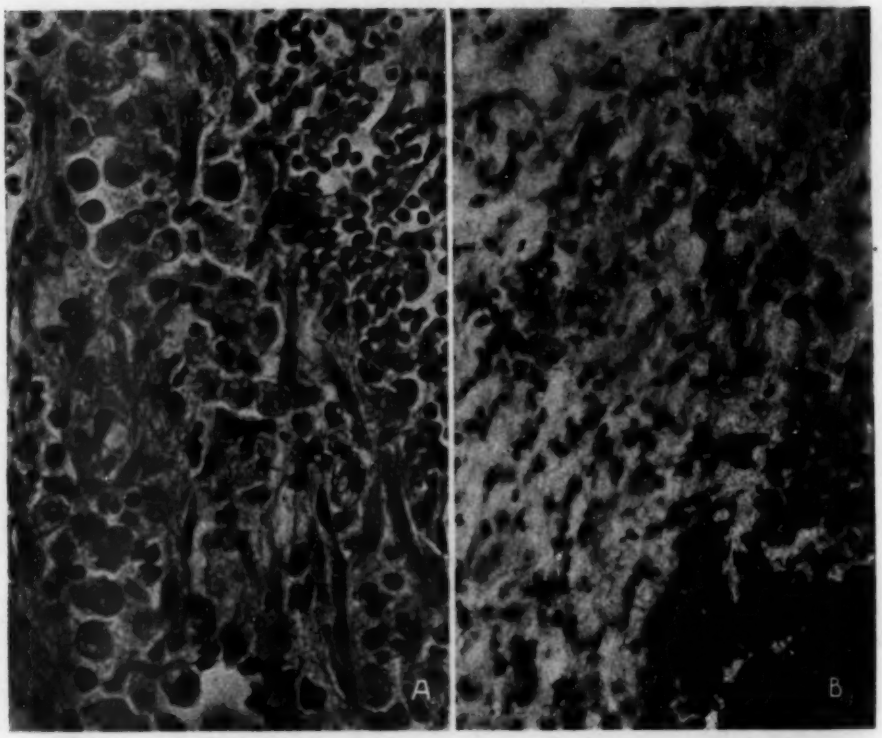

Fig. 5.—(*a*) Reticuloendothelial hyperplasia in a normal lymph node; × 350. (*b*) Fat globules without adult fat cells in thymoma; sudan III; × 285.

but that the interrelationships of the several lymphoid structures in regard to volume are statistically insignificant.

An attempt was made to correlate the clinical findings, the severity and duration of symptoms and the improvement following surgical intervention with the presence of microscopic and gross evidence of hyperplasia, but there was no correlation in this series; consequently it seems that the pathologist cannot, by gross or microscopic examination, either ascertain the clinical course preoperatively or prognosticate the results

of surgical treatment. Keynes [39] stated that the prognosis is better in cases in which there is a history of short duration of the condition and poorer in cases in which the disease is of long duration or in which there is a tumor. His colleagues, Collins and Bratton,[40] have investigated thymus glands from normal adults and adults with myasthenia gravis, and they have found it not easy to detect any constant difference between them; they have expressed the belief that in most myasthenic glands there is an abnormal development of foci of clear cells resembling the so-called germinal centers of lymph nodes.

Thymoma.—It was observed in the preliminary study of the thymoma group that differentiation from extreme hyperplasia is not always easy and that none of the histologic criteria used in diagnosis are constant or limited to cancers or thymoma. Similar kinds and numbers of Hassall's corpuscles, calcium, hyalinized trabeculae, lining up of cells along trabeculae, perivascular grouping, necrosis, foam cells and mitotic figures may be found in fetal, normal and hyperplastic thymuses.

However, one of us (J. R. M.) has shown that fat is rarely found in the thymus afflicted with thymoma. An analogous situation is found in the hyperplastic parathyroid gland and the parathyroid adenoma, the latter rarely containing any adult fat cells. There are a few other constant features of thymoma; namely, it is usually encapsulated, it usually exhibits excessively thickened trabeculae and it usually has distorted thymic structure. In one of the specimens of thymoma, after diligent examination, a few adult fat cells were found, but these may well have represented extracapsular extension of the tumor. A section of thymoma stained with sudan III and showing fat globules but no adult fat cells is illustrated in figure 5 *b*.

A descriptive definition of thymoma might be phrased as follows: Thymoma is a circumscribed tumor of the thymus composed of structurally disarranged thymic elements, often with dense dividing trabeculae, and usually devoid of adult fat cells.

SUMMARY

Among 23 proved cases of myasthenia gravis, exclusive of thymoma, in which thymectomy was done, there were 4 in which extreme lymphoid hyperplasia, and 2 in which moderate lymphoid hyperplasia of the thymus, was observed on microscopic examination. In the remainder of the cases the gland either was normal or had been replaced by fat.

Twelve of the 17 normal glands in the myasthenia series showed areas of hyperplasia, but the percentage of glandular tissue was too

39. Keynes, G.: Brit. J. Surg. **33**:201, 1946.
40. Collins and Bratton, cited by Keynes.[39]

low to permit their being considered hyperplastic, the average content of thymic parenchyma being only 29 per cent.

In none of the 20 cases of hyperthyroidism due to exophthalmic goiter did extreme hyperplasia of the thymus occur, and in only 1 case did moderate lymphoid hyperplasia occur.

Small areas of epithelial clustering occurred in 2 cases of the myasthenia series and in 3 cases of the hyperthyroidism series, but the glands were essentially normal.

When the actual amounts of the glandular tissue of the thymuses were determined and compared with Hammar's weights and with planimetrically determined percentages of thymic tissue, the weight of the parenchyma of 2 of 13 glands in the myasthenia series significantly exceeded the upper limit of normal, while the weight of the parenchyma of 7 of 9 glands in the hyperthyroidism series exceeded the upper limit of normal.

There was apparently no correlation between the extent of hyperplasia determined microscopically and that which was observed when the actual weight of essential thymic elements exceeded significantly the expected upper limit of normal.

There was no correlation, on the basis of microscopic observations, between the extent of hyperplasia of one lymphoid organ and that of another in this study.

No correlation was found between the clinical and the microscopic observations in myasthenia gravis exclusive of thymoma.

The term "thymoma" might be defined as a circumscribed tumor of the thymus composed of structurally disarranged thymic elements, often with dense dividing trabeculae, and usually devoid of adult fat cells.

TESTICULAR TUMORS

II. Interstitial Cell and Miscellaneous Neoplasms

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AND
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IN A PREVIOUS communication [1] a simple classification of testicular neoplasms was proposed, and the commonly occurring seminoma and teratoma were discussed from clinical and pathologic points of view. The present report completes the study of testicular tumors, dealing with the interstitial cell and rare miscellaneous types, which together constitute less than 5 per cent.[2] A number of important contributions in the literature are reviewed. Four cases collected in a review of the files of the department of pathology of the Peter Bent Brigham Hospital from 1914 to 1947 are reported.

MATERIAL AND METHODS

The material consisted of blocks taken from surgically excised primary tumors and metastatic lesions, fixed in Zenker's acetic acid solution and/or 4 per cent formaldehyde solution, embedded in paraffin and stained with eosin–methylene blue and/or hematoxylin and eosin. Fat and connective tissue stains were done when indicated.

CLASSIFICATION

The classification presented now is based on limited personal experience and an incomplete, albeit extensive, review of reported cases; hence, it is necessarily subject to errors of omission.

1. Arrhenoblastoma
2. Interstitial cell tumor
3. Adrenal cortex rest tumor
4. Tubular "adenoma"

From the Departments of Pathology of the Peter Bent Brigham Hospital and Harvard Medical School and the Department of Surgery of the Peter Bent Brigham Hospital. Dr. Scully's present address is: Pondville Hospital, Walpole, Mass.

1. Scully, R. E., and Parham, A. R.: Arch. Path. **45**:581, 1948.
2. Friedman, N. B., and Moore, R. A.: Mil. Surgeon **99**:573, 1946.

5. Adult carcinomas
   (*a*) Spermatocytic seminoma [3]
   (*b*) Multicystic adenocarcinoma [4]
   (*c*) Carcinoma of rete testis
6. Tumors of blood vessel origin
7. Tumors of fibrous tissue origin
8. Lymphosarcoma
9. Metastatic tumors

ARRHENOBLASTOMA

Teilum [5] has reported 3 tumors occurring in males which were histologically identical with Meyer's intermediate type of ovarian arrhenoblastoma.[6] One occurred in the testicle of a 53 year old man who complained of gynecomastia and presented a history of left scrotal swelling, diminution of libido and loss of potency. After orchidectomy the mammae decreased greatly in size. The second tumor was situated in the spermatic cord of a 4 year old boy who showed no endocrine disturbances. The third was testicular; clinical data regarding it were not available.

INTERSTITIAL CELL TUMOR

Pathologic Aspects.—The interstitial cell tumor is typically nodular and yellowish or yellowish brown [7]; it may or may not be encapsulated [8]; reported specimens have varied from less than 2 cm. in diameter to the dimensions of a child's head.[8]

Microscopically, the large polyhedral cells grow in sheets, cords and lobules, separated by varying amounts of collagenous stroma (fig. 1 *A*); at times columns of cells lie in intimate relation to thin-walled vascular sinusoids, creating a liver-like appearance. The cytoplasm of the neoplastic cells is voluminous and eosinophilic (fig. 1 *B*); it may be loaded with fine fat droplets, or the latter may be dispersed in the form of peripheral halos. Intracytoplasmic lipofuchsin granules are commonly present; Reinke's crystalloids, the characteristic inclusions of the normal interstitial cell, rarely.[9] The neoplastic nuclei are round, oval or wrin-

3. Masson, P.: Rev. canad. de biol. **5**:361, 1946.

4. (*a*) Stevens, A. R., and Ewing, J.: Ann. Surg. **88**:1074, 1928. (*b*) Stofer, B. E.: Arch. Path. **40**:68, 1945.

5. Teilum, G.: (*a*) Acta obst. et gynec. Scandinav. **24**:480, 1944; (*b*) Acta path. et microbiol. Scandinav. **23**:252, 1946.

6. Meyer, R.: Am. J. Obst. & Gynec. **22**:697, 1931.

7. Nation, E. F.; Edmondson, H. A., and Hammack, R. W.: Arch. Surg. **48**:415, 1944.

8. Warren, S., and Olshausen, K. W.: Am. J. Path. **19**:307, 1943.

9. Friedman, N. B., and Ash, J. E.: Atlas of Genitourinary Pathology Prepared at the Army Institute of Pathology, Washington, D. C., Government Printing Office, 1946.

kled and contain one or more prominent nucleoli. Mitoses are generally absent but may be abundant.[7]

Rarely the interstitial cell tumor gives rise to metastases; moreover, the latter may occur years after removal of a primary tumor which appeared histologically benign.[10]

Endocrinologic Aspects.—A recent collective review of 26 cases by Nation and co-workers [7] reveals that in 9 cases the tumor was associated with clinical evidence of hormone imbalance. All 6 children in the series showed precocious bodily and sexual development; gynecomastia [11] was present in 1. Orchidectomy was followed by partial or complete regression of symptoms in 4. Gynecomastia occurred in 3 of 20 adults; in 2 it regressed postoperatively. One adult experienced a decrease in libido, which returned to normal after orchidectomy.[12] No correlation was found between the duration of the tumor and the postoperative regression of the hormonal changes.

Reports of assays of hormones have been few. In a case of cancerous interstitial cell tumor reported by Masson [10] and Venning [13] there was slight elevation of urinary gonadotropin and estrogens, and a marked rise in 17-ketosteroids. In the case to be reported, no endocrine changes were evident clinically, nor were assays of hormones made.

Clinical Aspects.—In the large series of Friedman and Moore [2] the interstitial cell growths constituted 1 per cent of the testicular tumors. Persons of all ages are affected; in adults the maximum incidence is between the ages of 30 and 45,[7] while in children the onset tends to occur during the fourth or the fifth year of life.[7]

Metastases have been reported in 3 cases,[8] in one appearing four,[14] and in another nine years,[10] after removal of the primary tumor. The interstitial cell tumor to be reported occurred in a 55 year old man, who was free of metastases ten years seven months after the operation.

Case 1.—H. M., a 55 year old white man, complained of swelling of the left testicle of two years' and testicular pain of five days' duration. Physical examination revealed a grapefruit-sized testicular mass, acutely tender on its inferolateral surface. There was no gynecomastia. Orchidectomy was performed. Death occurred ten years seven months later, due to heart disease. No evidence of tumor was found at autopsy.

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10. Masson, P.: Rev. canad. de biol. **1**:570, 1942.

11. Gynecomastia secondary to a testicular neoplasm may not necessarily be of estrogenic origin; evidence exists that androgens may likewise stimulate mammary growth.

McCullagh, E. P., and Rossmiller, H. R.: J. Clin. Endocrinol. **1**:496, 1941.

12. Hunt, V. C., and Budd, J. W.: J. Urol. **42**:1242, 1939.

13. Venning, E. H.: Rev. canad. de biol. **1**:571, 1942.

14. Masson, P., and Sencert, L.: Bull. Assoc. franç. p. l'étude du cancer **12**:555, 1923.

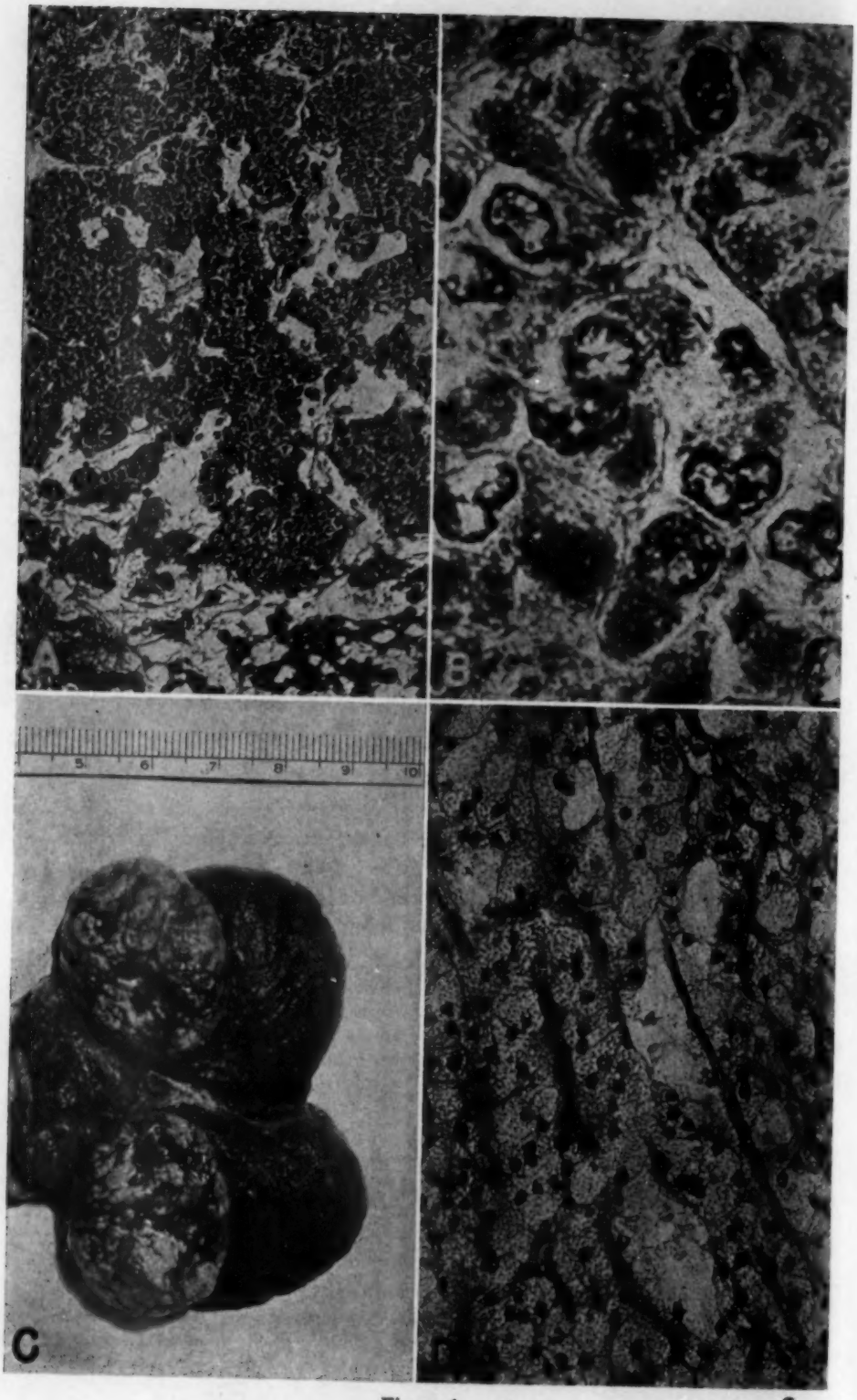

Figure 1

(See legend on opposite page)

The tumor, epididymis and cord weighed 305 Gm. The tumor measured 8 cm. in diameter; it was spherical and encapsulated. On section it was soft and slightly resilient and was composed of translucent grayish tissue lobulated by fibrous trabeculae. Large amounts of clotted blood were present. At the periphery was a rim of opaque yellow tissue. Microscopically, the tumor was composed of cords and sheets of polyhedral cells arranged along blood-containing sinusoid spaces (fig. 1 *A*). The cells were characterized by slightly granular acidophilic cytoplasm so distributed as to form a dense centrum surrounded by a narrow pale halo (fig. 1*B*).[15] The cell borders were distinct. Occasional cells contained small yellow-brown globules in their cytoplasm. The nuclei were oval, bent or wrinkled, and frequently eccentric; they contained a finely beaded reticulum of chromatin and usually one prominent nucleolus. Occasional mitoses were observed.

ADRENAL CORTEX REST TUMORS

Adrenal cortex rests are common in the vicinity of the epididymis. Although Glynn [16] was able to find but one report of aberrant adrenal tissue within the testis proper, Friedman and Ash [9] stated that such inclusions are frequent.

The identification of adrenal rest neoplasms in the testis is extremely difficult, owing to the striking resemblance of adrenal and interstitial cells. In general, morphologic or endocrinologic features regarded as atypical for the commoner Leydig cell tumor have constituted the criteria for diagnosis. In the following paragraphs are discussed three types of tumor which have been considered to be of adrenal cortex rest origin.

The first type is a rare testicular neoplasm composed largely of cells laden with tiny fat droplets (fig. 1 *D*) and bearing a striking resemblance to adrenal cortex. Although an origin from the latter cannot be excluded, the morphologic aspect is equally consistent with neoplasia of the Leydig cells, for the latter, both in tumors which show typical features elsewhere and in non-neoplastic testicles, may appear as polyhedral lipoid-laden cells. Case 2 of the present series (figs. 1 *C* and *D*) illustrates this type. The tumor with the morphologic characteristics of adrenal cortex occurred in a 36 year old man who experienced no clinically manifest endocrine disturbances. It is being classified descriptively as an adrenal cortex–like tumor of the testis; its origin is in doubt.

Since adrenal cortex neoplasms in males can secrete estrogens, one Leydig cell–like tumor of the testis [17] associated with an increase of

15. A fat stain could not be made, owing to the absence of formaldehyde-fixed material.

16. Glynn, E. E.: Quart. J. Med. **5**:157, 1911.

17. Ostergaard, E.: J. Clin. Endocrinol. **7**:438, 1947.

Fig. 1.—*A*, interstitial cell tumor (case 1), showing a trabecular pattern. Note wrinkled appearance of nuclei. × 200.

B, interstitial cell tumor (case 1), showing the characteristic dense granular cytoplasmic centrum and the clear peripheral halo. × 900.

C, adrenal cortex–like tumor (case 2). The bisected testicle presents an encapsulated tumor in the superior pole. Dark patches represent areas of hemorrhage.

D, adrenal cortex–like tumor (case 2). × 400.

the estrogen excreted in the urine has been regarded as of adrenal rest origin (second type). Again, however, interstitial cell neoplasia cannot be excluded, since the ability of this cell to produce estrogens is at present undetermined.

Two recently reported bilateral testicular neoplasms [18] present greater claim to authenticity as adrenal rest tumors (third type). These, occurring in males with precocious somatic and genital development, were accompanied by hyperplasia of the adrenal cortex. In each case the neoplastic testicular cells were similar in appearance to the hyperplastic cortical cells. Although in one case [18a] they contained small amounts of lipid in fine droplets, the tumor cells were characterized by granular cytoplasm and were not of the lipoid-laden type.

CASE 2 (adrenal cortex-like tumor of testis).—F. L., a 36 year old white man, complained of pain in the left testicle following trauma two months prior to admission. The pain disappeared temporarily but recurred one month later. Physical examination revealed a firm, tender testis one-third larger than normal. No gynecomastia was present. An Aschheim-Zondek test was "slightly positive" on one occasion and negative on another. Orchidectomy was performed. The patient is alive and well eight years three months after the operation.

The testis, cord and epididymis weighed 40 Gm. The superior pole of the testis contained a round, encapsulated, bright orange-yellow, soft tumor showing focal areas of hemorrhage. It measured 3.3 by 2.7 by 2.0 cm. (fig. 1 *C*).

Microscopically, the tumor was composed of a diffuse mass of large polyhedral cells supported by a rich capillary network (fig. 1 *D*). At several points islands of tumor cells were present within the thick capsule composed of hyalinized fibrous tissue. In the larger portion of the tumor the cytoplasm of the cells was laden with tiny fat droplets; in other areas, however, it was densely eosinophilic and free of visible fat. Occasionally a dense centrum of eosinophilic cytoplasm was surrounded by fine peripheral vacuoles. No intracytoplasmic pigment was visible. The tumor nuclei were small, round or oval, and pale, and frequently contained single, fine nucleoli. No mitoses were observed.

TUBULAR "ADENOMA"

The tubular "adenoma" occurs solely in the cryptorchid testicle, where it appears as single or multiple discrete white or yellow nodules. It may have microscopic dimensions or attain the size of a bean.[19]

Histologically one encounters closely packed small tubules lying in a scant stroma which may or may not contain Leydig cells (fig. 2). Lining the tubules are cylindric cells with loose granular cytoplasm and crowded oval or elongated nuclei. In a number of cases smaller round cells lie compressed between the taller elements.[20] The proliferating

18. (*a*) Cohen, H.: Am. J. Path. **22**:157, 1946. (*b*) Wilkins, L.; Fleischmann, W., and Howard, J. E.: Endocrinology **26**:385, 1940.

19. Ewing, J.: Neoplastic Diseases: A Treatise on Tumors, Philadelphia, W. B. Saunders Company, 1940.

20. Chevassu, M.: Tumeurs du testicule, Thesis, Paris, no. 193, Paris, G. Steinheil, 1906.

cells may obliterate the tubular lumens, or, on the other hand, may surround small oval or star-shaped openings. Not infrequently the latter contain casts of amphophilic colloid-like material. Transitional stages from adenoma tubules to atrophic tubules lined by typical Sertoli cells are observable in the adjacent parenchyma.

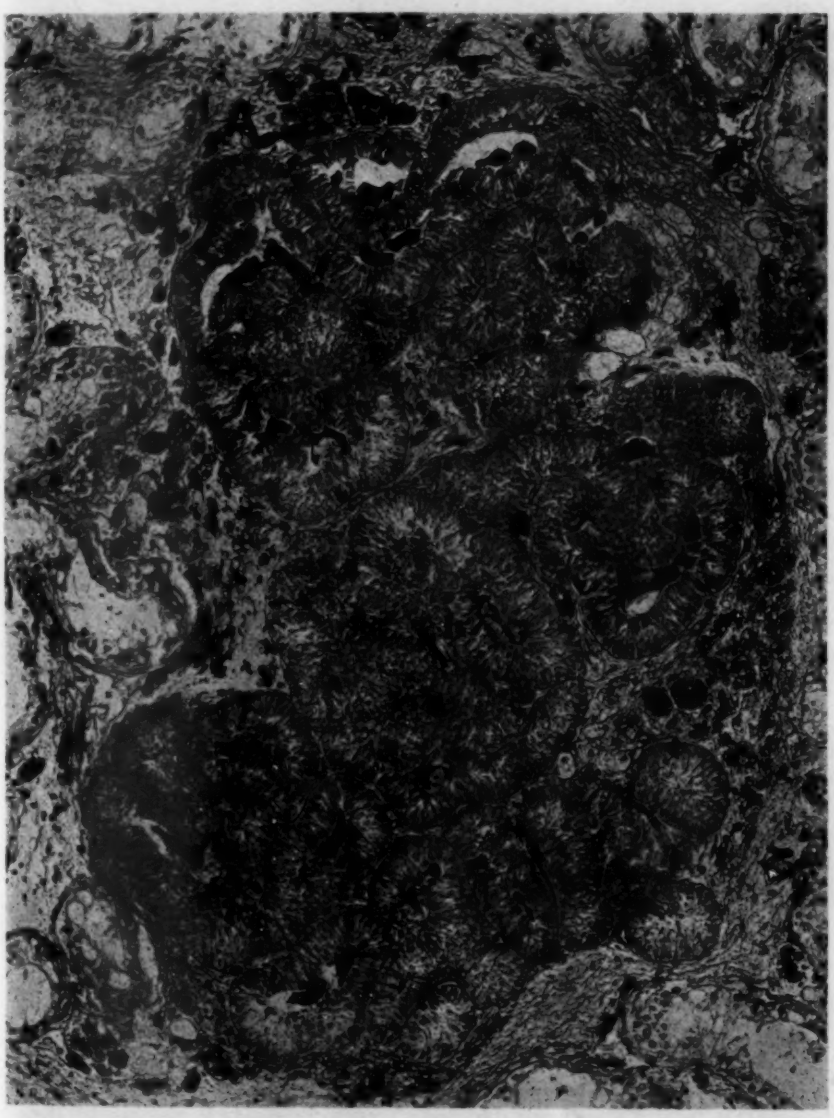

Fig. 2.—Testicular adenoma in a cryptorchid testis. The tubules of the adenoma contain basophilic colloid. Numerous collections of Leydig cells are present (e.g., at *A*). The surrounding testis shows atrophy and fibrosis. Sertoli cells containing large lipoid vacuoles line the atrophic tubules. × 150.

The testicular adenoma is of no clinical significance; cancerous transformation has not been reported. Since, in addition, microscopic examination of undescended testicles frequently reveals the presence of adenoma tubules occurring singly as well as in clusters, the designation of these lesions as true tumors appears unjustifiable.[21]

ADULT CARCINOMAS

A small number of testicular carcinomas free of teratomatous elements and composed of cells lacking the staining properties which characterize embryonal cells have been reported. Of these, the tumor of Waterman and Brines,[22] composed of faintly basophilic cells arranged in cords with occasional lumen formation, offers no clues as to its origin. The ones described by Bell,[23] which have been accepted elsewhere [4] as adult carcinomas, we believe may be embryonal, since the author characterizes each as having cells of the germinal type; the published photomicrographs unfortunately are at too low a magnification to enable one to interpret accurately the morphologic features of individual cells.

Adult carcinomas which present evidence of having arisen from the spermatogenic epithelium, the Sertoli cell and the rete epithelium likewise rarely occur.

Spermatocytic Seminoma.—Masson [3] has observed 6 round cell carcinomas of the testis which differ from the classic seminoma by the irregularity and smaller size of their cells, their lack of cytoplasmic glycogen and the scantiness of their stroma, which is free of lymphoid infiltration. The striking resemblance of the cells to spermatogenic cells, the marked tendency to invade the seminiferous tubules and the observation in 1 case of the genesis of a neoplastic focus within a tubule are presented as evidence of origin from male germinal epithelium.

Multicystic Adenocarcinoma (? Sertoli Cell Carcinoma).—The adult carcinomas of Stevens and Ewing [4a] and Stofer [4b] in addition to solid neoplasia exhibited a papillary cystic pattern closely simulating rete testis. The former tumor grossly spared the rete; in the belief that it arose from adult seminiferous epithelium it was termed adult multicystic adenocarcinoma.

In the present series a similar carcinoma showing diffuse, trabecular and papillary cystic patterns (figs. 3 *A, B* and *D*) was encountered in a 60 year old man. Two features of this tumor favored its being inter-

21. Genuinely neoplastic tubular adenomas, which may be histologically indistinguishable from the testicular "adenoma" occur, however, in the ovary; there they are often associated with masculinization.

22. Waterman, J. L., and Brines, O. A.: U. S. Nav. M. Bull. **41**:1690, 1943.

23. Bell, P. G.: Brit. J. Surg. **13**:282, 1925.

preted as a Sertoli cell carcinoma: 1. In numerous tumor cells in the solid portions were large vacuoles of variable size separated by networks of cytoplasmic septums (fig. 3 *C*). This appearance recalled that of Sertoli cells in atrophic testicular tubules. Likewise, intracellular fat vacuoles of similar dimensions are prominent in Sertoli cell carcinomas occurring in dogs.[24] 2. In the lumens of the cystic spaces and within a number of the lining cells were globules of amphophilic colloid material (fig. 3 *D*) not unlike that present in the tubular lumens in Sertoli cell adenoma (fig. 2).

If we exclude the so-called testicular adenomas, tumors of Sertoli cell origin have not to our knowledge been described as such occurring in man. They are, however, of not infrequent occurrence in dogs, in which they may be associated with clinical estrogenic manifestations, and in a number of cases an estrogenic substance has been extracted from them.[24] Despite this strong evidence that the Sertoli cell may secrete estrogens, histochemical studies done on the testes of mammals other than man and dog have failed to indicate the presence of steroid hormones elsewhere than in the Leydig cells.[25] In the present case no light is shed on the problem since there was no clinical evidence that estrogen was secreted by the tumor, nor were assays of hormones made.

Case 3.—M. F., a 60 year old white man complained of painless swelling of the right testicle of two months' duration. Physical examination revealed a firm, nontender mass in the right scrotum, the size of a double fist. There was no gynecomastia. Orchidectomy was performed. The patient had been symptom-free for approximately three and a half years, when he was admitted to an outside hospital for gastrointestinal complaints and loss of weight. Death occurred from extensive metastatic disease four years eight months after the operation. No biopsy of metastatic lesions or autopsy was performed.

At operation a hydrocele was encountered. The tunica vaginalis was studded with numerous tumor nodules. The testis and epididymis were almost entirely replaced by a hard mass, glistening and yellowish white on the cut surface and twice the size of a normal testicle.

Microscopically the tumor was composed in large part of irregular sheets, cords and strands of epithelial cells separated by abundant collagenous stroma (fig. 3*A* and *B*). The cytoplasm of the neoplastic cells was eosinophilic and nongranular and varied in amount from scant to abundant; often it became condensed to form intracellular hyaline globules, while in some areas droplets and pools of eosinophilic hyaline material lay among the cells. A striking feature was the presence in numerous cells of large round vacuoles [26] separted by thin cytoplastic septums (fig. 3 *C*). The tumor nuclei varied widely from small round or oval to larger irregular forms; the latter were oval or bent and frequently eccentric. The chromatin was granular and abundant, and numerous mitoses were present. One portion of the

24. Huggins, C., and Moulder, P. V.: Cancer Research **5**:510, 1945.

25. Pollock, W. F.: Anat. Rec. **84**:23, 1942.

26. A fat stain could not be made, owing to the absence of formaldehyde-fixed material.

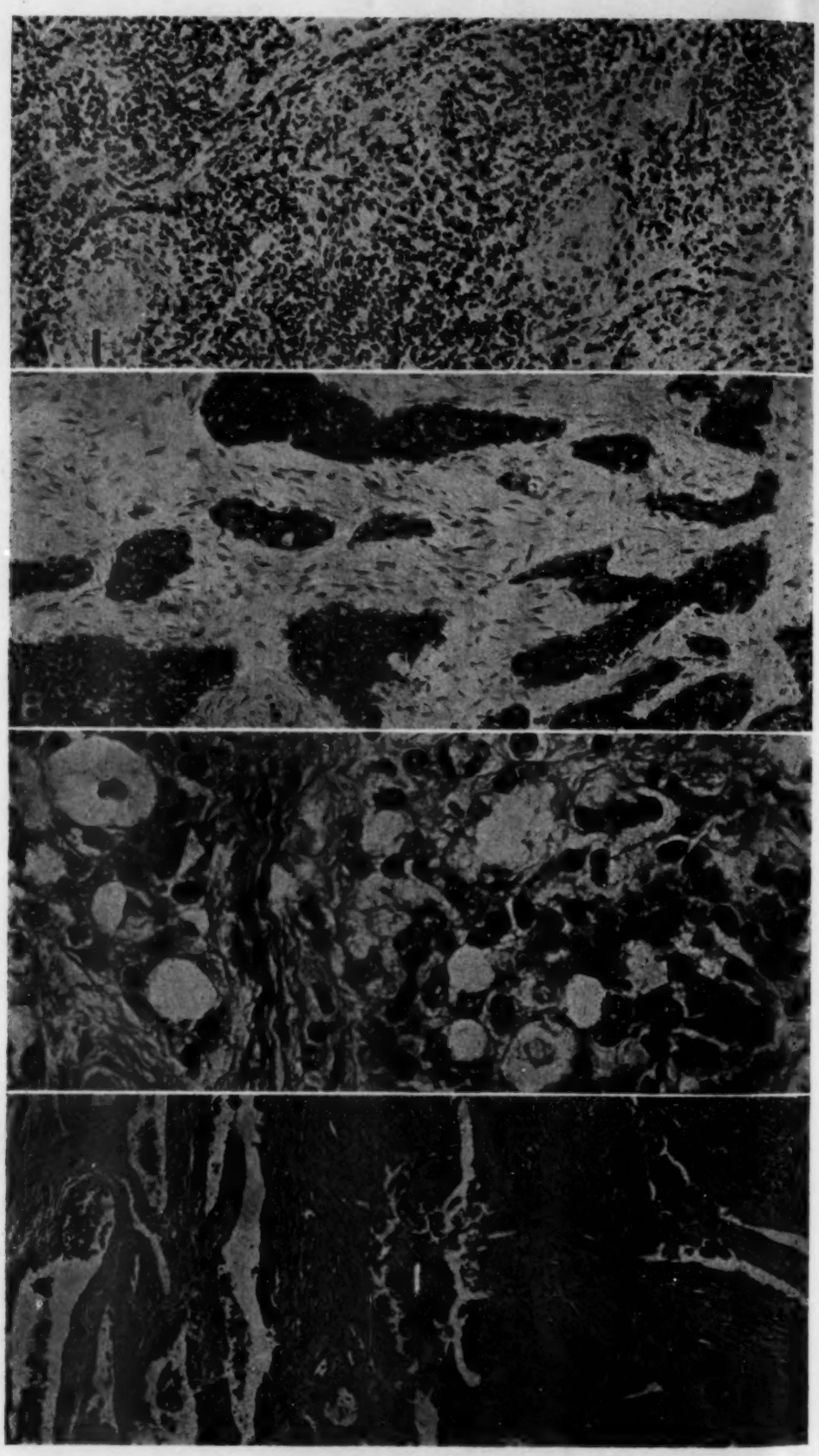

Figure 3

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tumor consisted of many intercommunicating elongated cystic tubules into which projected single and anastomosing papillary projections of dense stroma (fig. 3 *D*). The cysts were lined by simple flat to columnar or stratified tumor cells. The nuclei of the latter were in general more mature than those of the solid portion, being relatively uniform, oval or elongated, and pale; only occasional mitoses were encountered. In the lumens of the cystic spaces and within a number of the lining cells were large globules of amphophilic colloid-like material (fig. 3 *D*). This resembled closely the eosinophilic material observed in the solid portion of the tumor.

Numerous nests of tumor cells were present within lymphatic channels.

Carcinoma of Rete Testis.—Feek and Hunter[27] have reported an adult carcinoma of a 59 year old man showing transitions from rete tubular epithelium to a papillary carcinomatous pattern. In the present series an adenocarcinoma radiating from the hilus into the testicular parenchyma (fig. 4 *A*) was encountered in a man 48 years of age. The manner of growth, from both gross and microscopic points of view, was that of a primary neoplasm; furthermore, the gross localization of the tumor, as well as the microscopic appearance of irregular elongated tubules lined by cells resembling rete epithelium, indicated that an origin from the latter was most probable.

Case 4.—Y. S., a 48 year old white man, complained of low back pain that radiated down the right leg of five months' duration. The testicles were not abnormal to palpation. Roentgen examination revealed atelectasis of the middle lobe of the right lung. Bronchoscopic examination showed narrowing of the bronchi of the middle and lower lobes of the right lung but no evidence of intrinsic bronchial tumor. An expanding destructive lesion of the ninth rib, which became apparent by roentgenogram seven weeks after admission, was excised. Pathologic examination showed an adenocarcinoma which was simultaneously osteolytic and osteoblastic. Eleven weeks after admission the right testicle became painful, tender and swollen. Physical examination now revealed a hydrocele and a stony-hard testicular mass. An Aschheim-Zondek test was negative. Bilateral orchidectomy was performed. The patient died ten months later with extensive metastatic disease which had been resistant to roentgen therapy. No autopsy was performed.

Pathologic examination of the neoplastic testis revealed a sharply circumscribed, pale brown, scirrhous mass measuring 3 by 1.7 by 2.2 cm. and radiating from the hilus into the parenchyma (fig. 4 *A*). Microscopically, irregular elongated acini separated by abundant loose, poorly cellular collagenous stroma, infiltrated extensively between atrophic testicular tubules (fig. 4 *B*). The tumor cells were cuboidal or peg-shaped and were characterized by abundant eosinophilic cytoplasm

27. Feek, J. D., and Hunter, W. C.: Arch. Path. **40**:399, 1945.

Fig. 3.—*A*, multicystic adenocarcinoma of the testis (case 3), showing a diffuse pattern. Abundant collagen is present between groups of tumor cells and between individual tumor cells. Several sclerosed seminiferous tubules remain intact (e.g., at *1*). × 200.

B, multicystic adenocarcinoma of the testis (case 3). The tumor nests are isolated by fibrous stroma. × 200.

C, multicystic adenocarcinoma of the testis (case 3). The tumor cells contain various-sized round vacuoles separated by cytoplasmic septums. × 800.

D, multicystic adenocarcinoma of the testis (case 3). A papillary cystic portion is seen. Note the globules of colloid in the small cyst to the left of *1*. × 100.

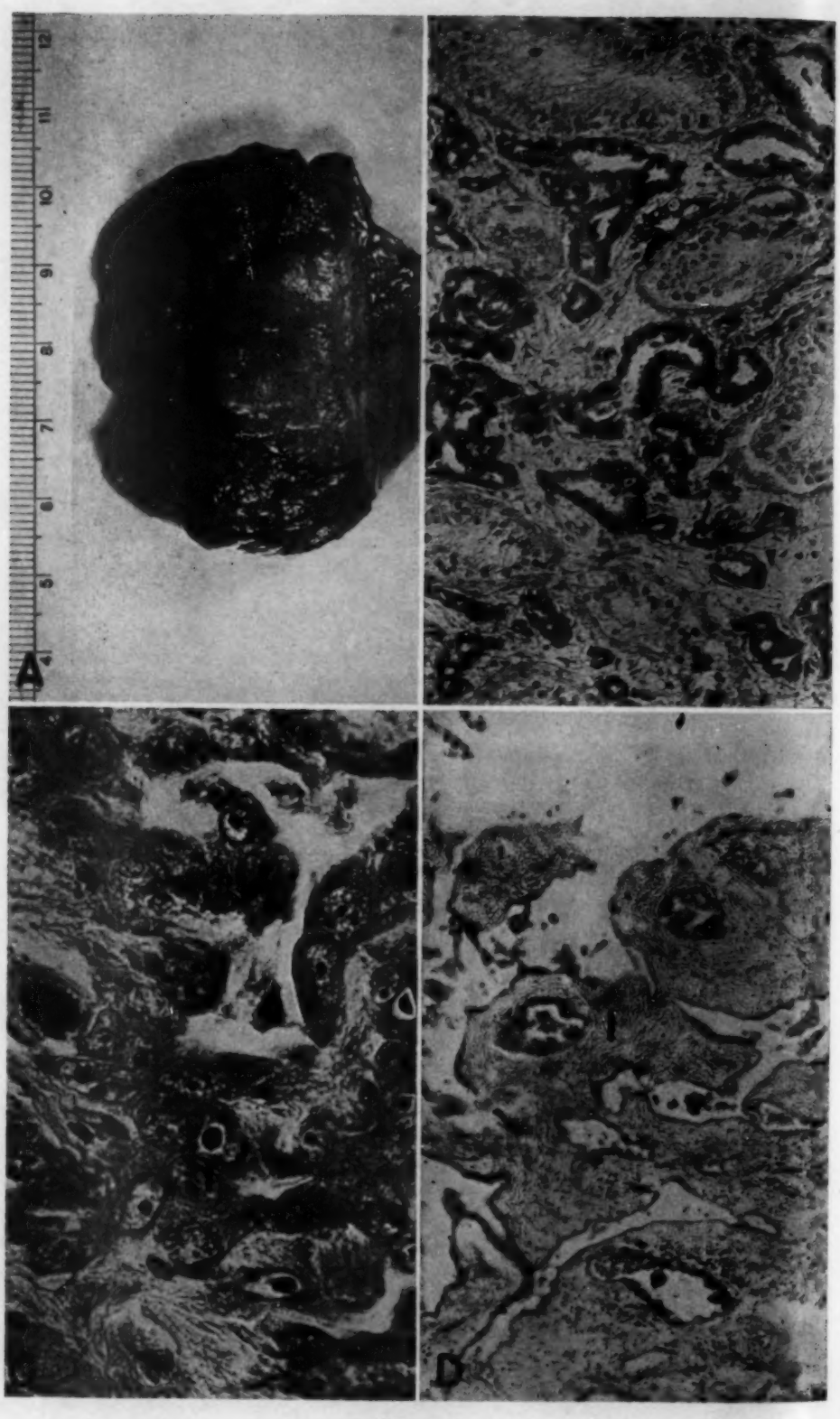

Figure 4

(See legend on opposite page)

and round to oval nuclei containing single or double prominent central nucleoli (fig. 4 *C*). Large, irregular, hyperchromatic nuclei and mitotic forms were not infrequent. The cytoplasm of numerous cells enclosed various-sized round or irregular, dark brown or eosinophilic globules surrounded by clear halos (fig. 4 *C*). In the mediastinum testis were numerous tumor acini, lying among and at times penetrating the rete tubules (fig. 4 *D*). There was no evidence of tumor originating directly from rete epithelium in the sections examined; however, in some areas the rete cells had undergone hypertrophy and strongly resembled the tumor cells.

VASCULAR AND FIBROBLASTIC TUMORS

The rare tumors of the vascular system and of the connective tissue framework of the testis have been reported and collected by Rosenthal [28] and Chevassu,[29] respectively.

LYMPHOSARCOMA

Lymphosarcoma of the testis occurs rarely in children and adults; it is frequently bilateral. Occasionally, there is associated lymphosarcoma of the skin.[29] Although the normal testis is stated to contain no lymphoid tissue,[19] tumors of such tissue which appear to have been primary in the testis have been reported.[30]

METASTATIC TUMORS

Metastases of tumors are rarely observed in the testicle, a survey of the literature by Helfert and Pinck [31] disclosing less than 50 instances. Willis [32] lists three routes by which neoplasms may spread to the testicle: (1) the veins, with retrograde extension or venous embolism, (2) the lymphatic channels, with retrograde extension, and (3) the arteries, with arterial embolism. The first route has been reported in cases of cancer of the left kidney; the second, in cases of neoplasm involving the retroperitoneal nodes. The most commonly reported artery-borne metastasis is the melanoma.

28. Rosenthal, A. A.: J. Urol. **55**:542, 1946.
29. Dockerty, M. B., and Priestly, J. T.: J. Urol. **48**:514, 1942.
30. Mathe, C. P.: J. Urol. **55**:530, 1946.
31. Helfert, I., and Pinck, B. M.: J. Urol. **51**:635, 1944.
32. Willis, R. A.: The Spread of Tumors in the Human Body, London, J. & A. Churchill, 1934.

Fig. 4.—*A*, adenocarcinoma of the rete testis (case 4). A cut surface of the testicle, sectioned in the sagittal plane, shows a discrete tumor mass radiating from the region of the rete.

B, adenocarcinoma of the rete testis (case 4). Irregular elongated tumor acini infiltrating between atrophic seminiferous tubules. × 200.

C, adenocarcinoma of the rete testis (case 4). The tumor cells are characterized by abundant dense cytoplasm and nuclei containing prominent nucleoli. Several dense intracytoplasmic globules surrounded by clear halos are visible (e.g., at *1*). × 800.

D, adenocarcinoma of the rete testis (case 4). Tumor acini are seen among the rete tubules (e.g., to the left of *1*). × 75.

A review of all cases from 1914 to 1947 in which autopsy was performed on a male dying of a cancerous disease other than an intracranial neoplasm at the Peter Bent Brigham Hospital (over 600 cases) disclosed only 1 case in which a metastatic growth was grossly detectable in a testicle. This was a lymphoma unassociated with a leukemic picture of the peripheral blood. Excluding leukemias, secondary microscopic involvement [33] of the testis was likewise exceedingly rare, occurring only in 2 cases, which were cases of multiple plasma cell myeloma; in each case the testicular infiltration was of the leukemic type.

SUMMARY

The interstitial cell tumor is discussed from clinical and pathologic points of view. One case is reported.

A large number of miscellaneous testicular neoplasms were collected in a fairly extensive, although incomplete, review of the literature; they are classified and discussed briefly.

Three rare tumors, an adrenal cortex–like tumor of the testicle, a multicystic adenocarcinoma and an adenocarcinoma of the rete testis, are reported.

33. Microscopic examination of one or both testicles was done in approximately 45 per cent of the total number of cases.

SOME PROBLEMS RELATED TO THE ORIGIN AND MEANING OF PITUITARY GLAND TUMORS

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IN THE course of several years, Dr. Clovis Vincent, neurosurgeon at the Pitié Hospital in Paris, and Drs. Clemente Robles and Mariano Vázquez, at the General Hospital, Mexico City, have been providing me with abundant material in addition to the routine specimens received in the department of pathology of the National Institute of Cardiology; this has enabled me to examine more than 3,000 intracranial tumors. Among these belong the 150 specimens of pituitary gland tumors which are the basis for the data presented in this paper. These data refer to the following matters: (1) the interpretation of the polymorphism of pituitary gland tumors; (2) the exhaustion of the acidophilic adenoma (oligochromic adenoma); (3) the polymorphism of the chromophobe adenoma (adenoepithelioma); (4) the solitary suprasellar cyst (archeoblastoma); (5) the limitation of the concepts of adamantinoma and teratoma.

INTERPRETATION OF THE POLYMORPHISM OF PITUITARY GLAND TUMORS

Pituitary gland tumors commonly offer difficulties for differential diagnosis because of their extreme cellular variety. In order to interpret correctly the character of the tumor cells in each case, and in order to recognize their reciprocal relations, it is necessary to review the genetic potentialities of the embryonal anlages of the hypophysis.

Rathke's pouch begins its development when the human embryo achieves the length of 3 mm. (Waterston [1]) and is found completely formed toward the fourth week of intrauterine life; the infundibulum appears in the 8 mm. embryo, and its juxtaposition with Rathke's pouch is completed in the 21 mm. embryo; a little later, when the embryo reaches the length of 32 mm., Rathke's pouch becomes definitely isolated from the oral cavity and forms the pituitary vesicle, which is lined by

From the Department of Pathology of the National Institute of Cardiology, and the University of Mexico School of Medicine.

1. Waterston, D.: Tr. Roy. Soc. Edinburgh **55**:125, 1926.

simple columnar epithelium; behind it lies the infundibulum, and the whole structure is correctly limited by a membrane formed by the meningeal covers.

The prostomic epithelium, which has been displaced so early into the skull base in order to form the pars buccalis of the hypophysis, conserves its multiple morphologic potentialities for a long time. These potentialities may develop in three manners: typically, atypically and abnormally (table 1).

I consider as typical potentialities those which determine the development of the pars buccalis sive glandularis of the hypophysis, involving (*a*) the formation of chromophobe, acidophilic and basophilic cells, which are normally found in the pars distalis, and (*b*) the conservation

TABLE 1.—*Potentialities of the Pituitary Vesicle*

Typical	(a) Formation of chromophobe, acidophilic and basophilic cells	Pars distalis
	(b) Conservation of cavities lined by either columnar, cuboidal or squamous epithelium which may or may not contain a colloid	Pars juxtaneuralis
Atypical	(c) Formation of pseudostratified or stratified columnar epithelium, with or without cilia, with or without tendency to secrete mucin	Hamartia
	(d) Formation of stratified squamous epithelium, with or without tendency to cornification	
	(e) Invagination of the epithelium with formation of simple or branched tubular glands, as well as acinotubular glands with or without tendency to secrete mucin	
Abnormal	(f) The epithelium of the pituitary vesicle conserves its simple columnar arrangement without forming cavities	Chorista
	(g) It induces formation of lymphoid follicles of tonsillar type in the adjacent connective tissue	
	(h) Likewise, it induces the formation of cartilage	
	(i) It transforms itself into enamel germs which may secrete a calcifiable albuminous substance	

of cavities lined by either columnar, cuboidal or squamous epithelium, which may or may not contain a colloid, as seen in the pars juxtaneuralis.

As atypical potentialities are considered (*c*) formation of pseudostratified or stratified columnar epithelium with or without cilia and with or without secreted mucin, (*d*) formation of stratified squamous epithelium with or without tendency to cornification and (*e*) invagination of the epithelium forming simple or branched tubular glands as well as acinotubular glands with or without tendency to secrete mucin. These three potentialities may become manifest in normal glands and represent a mistake of development, i. e., hamartia, according to Albrecht's nomenclature [2]; such structures are generally found in the pars juxtaneuralis and have a tendency to disappear gradually, so that they are common in children and rare in adults.

2. Albrecht, E.; Frankfurt. Ztschr. f. Path. **1**:221, 1907.

I consider as abnormal potentialities those which represent displacements of embryonal anlages, i. e., chorista, according to Albrecht, examples of which occur when (*f*) the epithelium of the pituitary vesicle conserves its simple columnar arrangement without forming cavities, (*g*) it induces formation of lymphoid follicles of tonsillar type in the adjacent connective tissue, (*h*) it likewise induces formation of cartilage and (*i*) it transforms itself into enamel germs which may secrete a calcifiable albuminous substance.

All the potentialities described in the foregoing paragraphs may appear in the tumors. The typical potentialities give rise to adenomas, while the atypical and abnormal ones manifest themselves chiefly in the tumors derived from the lining epithelium.

EXHAUSTION OF THE ACIDOPHILIC ADENOMA (OLIGOCHROMIC ADENOMA)

The existence of pituitary adenomas formed by cells similar to the eosinophilic cells of the normal hypophysis but containing small amounts of specific acidophilic substance has been pointed out by many authors. Poindecker [3] described the so-called pregnancy cell adenoma. Dott and Bailey [4] and Bailey and Davidoff [5] found that in many acidophilic adenomas the granulations were so weakly stained that their demonstration was difficult; in other tumors they observed that the number of granulated cells was small and that occasionally the specific granulations were absent as in the case of Poindecker's tumor. Kraus [6] called those tumors which contain few cells with typical acidophilic granulations transitional adenoma. Cushing [7] found a mixed variety of adenoma, formed in some parts by chromophobe elements and in others by cells with acidophilic granulations. All these forms have been placed together by Costero and Berdet [8] under the name of oligochromic adenoma; at the same time, they added the description of three histologic groups: exhausted acidophilic adenoma, grouped cell adenoma and megalocytic adenoma.

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3. Poindecker, H.: Wien. klin. Wchnschr. **26**:745, 1931.

4. Dott, N. M., and Bailey, P.: Brit. J. Surg. **13**:314, 1925.

5. Bailey, P., and Davidoff, L.: Am. J. Path. **1**:185, 1925.

6. Kraus, E. J., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8. p. 810.

7. Cushing, H.: Intracranial Tumors, Springfield, Ill., Charles C Thomas, Publisher, 1932.

8. Costero, I., and Berdet, H.: (*a*) An. Esc. nac. de cien. biol. **1**:67, 1938; (*b*) Estudio anatómico de 135 tumores de la hipófisis y dell tracto hipofisario, Monograph of the Sociedad Médica del Hospital General, México, 1939; (*c*) Gac. méd. de México **69**:286, 1939.

The study of a sufficient number of specimens suggests that, of all the morphologic types classified under the name of oligochromic adenoma, only these last three represent the terminal stages of three different types of evolution of acidophilic adenoma. Following this criterion, I consider them to be the only static or true oligochromic adenomas. Their characteristic features are described in the following paragraphs.

Apparently, the most common phenomenon is the gradual loss of the cellular capacity to elaborate specific granulations; in this way, the formation of the exhausted acidophilic adenoma is reached through several intermediate forms. To these forms belong some of those described by Dott and Bailey, the transitional adenoma of Kraus, and Poindecker's tumor.

Figure 1 reproduces, with low magnification, the aspect of a typical acidophilic adenoma in which the granulations have been stained by the method of Bensley. All the cells of the tumor appear with their cytoplasm obscured by the acidophilic substance. Note the density of the neoplastic parenchyma, the tendency of the individual cell to become polyhedral through pressure and the central position of the nucleus.

Figure 2 shows a transitional adenoma in which the cells have abundant granulations with little affinity for the acidophilic substance, as becomes apparent when their color is compared with the intensity of the staining of the red blood cells. Observe that the tumoral elements have the same dense disposition, polyhedral shape and central nucleus as those of the typical acidophilic adenoma.

Another variety of transitional adenoma is shown in figure 3; in this one, only a small number of cells contain specific granulations, and high magnification is necessary in order to demonstrate them in the photomicrograph. The position of the nucleus and the arrangement of the cells is the same as in the typical acidophilic adenoma.

The reason for emphasizing the arrangement and the shape of the cells in each instance is that, in my opinion, they permit one to ascertain with a sufficient degree of correctness the hormonal activity of the adenoma without resorting to specific staining for granules. It is sufficient to remember the following general rule: The progressive exhaustion of the capacity of the neoplastic cells for elaborating specific acidophilic granulations is announced by these three morphologic phenomena—looseness of the neoplastic parenchyma, formation of spheroidal cells with homogeneously acidophilic cytoplasm and displacement of the nucleus toward the periphery of the cytoplasm.

A good example of such morphologic changes is found in figure 4, reproducing an oligochromic adenoma of the variety described by Poindecker. The tumor is divided into lobules by the huge vessels in

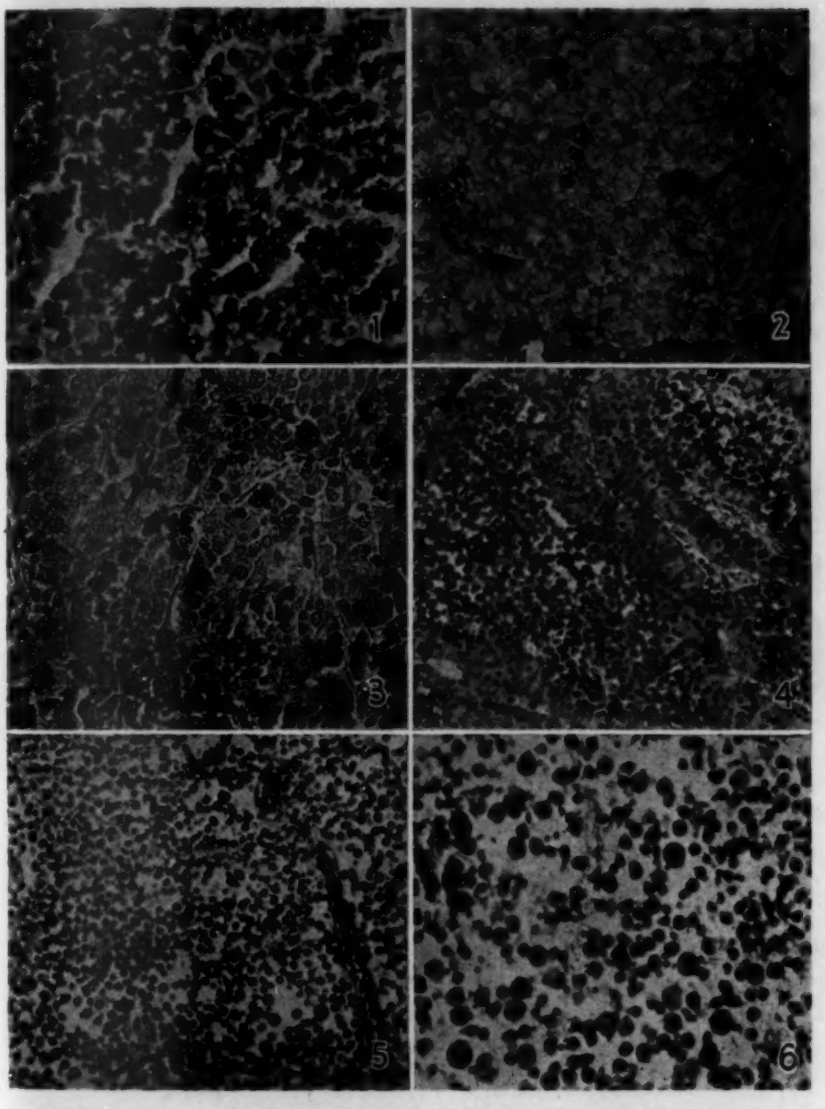


Fig. 1.—Typical acidophilic adenoma; Bensley's crystal violet and orange G stain; × 57.

Fig. 2.—Transitional adenoma in which the granulations have little affinity for the acidophilic substance; Bensley's crystal violet and orange G stain; × 57.

Fig. 3.—Transitional adenoma in which the capacity of the cells to produce acidophilic granulations is greatly reduced; Bensley's crystal violet and orange G stain; × 99.

Fig. 4.—Oligochromic adenoma of the variety described by Poindecker; hematoxylin and eosin; × 71.

Fig. 5.—Exhausted acidophilic adenoma; hematoxylin and eosin; × 28.

Fig. 6.—Exhausted acidophilic adenoma under higher magnification; hematoxylin and eosin; × 85.

the stroma. The cells lying close to the vessels have the form of a prism, and their cytoplasm shows intense acidophilia; the central portion of the lobules has loose arrangement and is formed by spheroidal cells in which the nucleus tends to take an eccentric position. The specific strains were unable to demonstrate any granulations in this tumor.

In the exhausted acidophilic adenoma all the cells have a rounded shape, an eccentric and frequently lobulated nucleus and limits sharply outlined, owing to the intense eosinophilia of the cytoplasm; they lie within an albuminous mass, in which they seem to float and which contains a delicate network of blood vessels. The general aspect of the slides when observed under low power (fig. 5) is more suggestive of a smear of bone marrow than of a section of a solid tissue. At higher magnification the histologic features described become apparent (fig. 6).

Megalocytic adenoma is rare, and this may be the reason why its histogenesis is difficult to understand. The tumor cells are much bigger than in any other variety of pituitary adenoma (fig. 7). The cytoplasm is intensely eosinophilic and homogeneously grumous; the nucleus, which is rarely lobulated, is constantly found in a peripheral position. The high density of the cellular arrangement makes the cells adopt a polyhedral shape with rounded edges. Under low power a slide of megalocytic adenoma has a certain similitude to a transverse section of striated muscle.

The arrangement of the large cells is due to the disposition of the blood vessels; thus it appears uniform and regular when the capillaries form a homogeneous network as in figure 7; when the vessels are parallel, the cells form long cords which anastomose like liver trabeculae (fig. 8).

I have not been able to find transitional forms between the typical acidophilic adenoma and the megalocytic adenoma. Probably the latter is formed by acidophilic elements which suddenly have lost their capacity for elaborating specific granulations; i. e., I suppose, the megalocytic adenoma is a frustrated form of acidophilic adenoma.

The grouped cell adenoma seems to originate by an exaggeration of the capacity of the acidophilic cells for elaborating interstitial albuminous substance. This capacity is already manifest in the exhausted adenoma and is comparable to that existing in the pars juxtaneuralis of the normal hypophysis. In the grouped cell adenoma (fig. 9) the stroma appears to be formed by a weakly and uniformly acidophilic colloid substance regularly interspersed between the tumor cells, which retracts a little with the substances used in histologic technics. The cells are arranged in small "isogenic groups" in a characteristic manner.

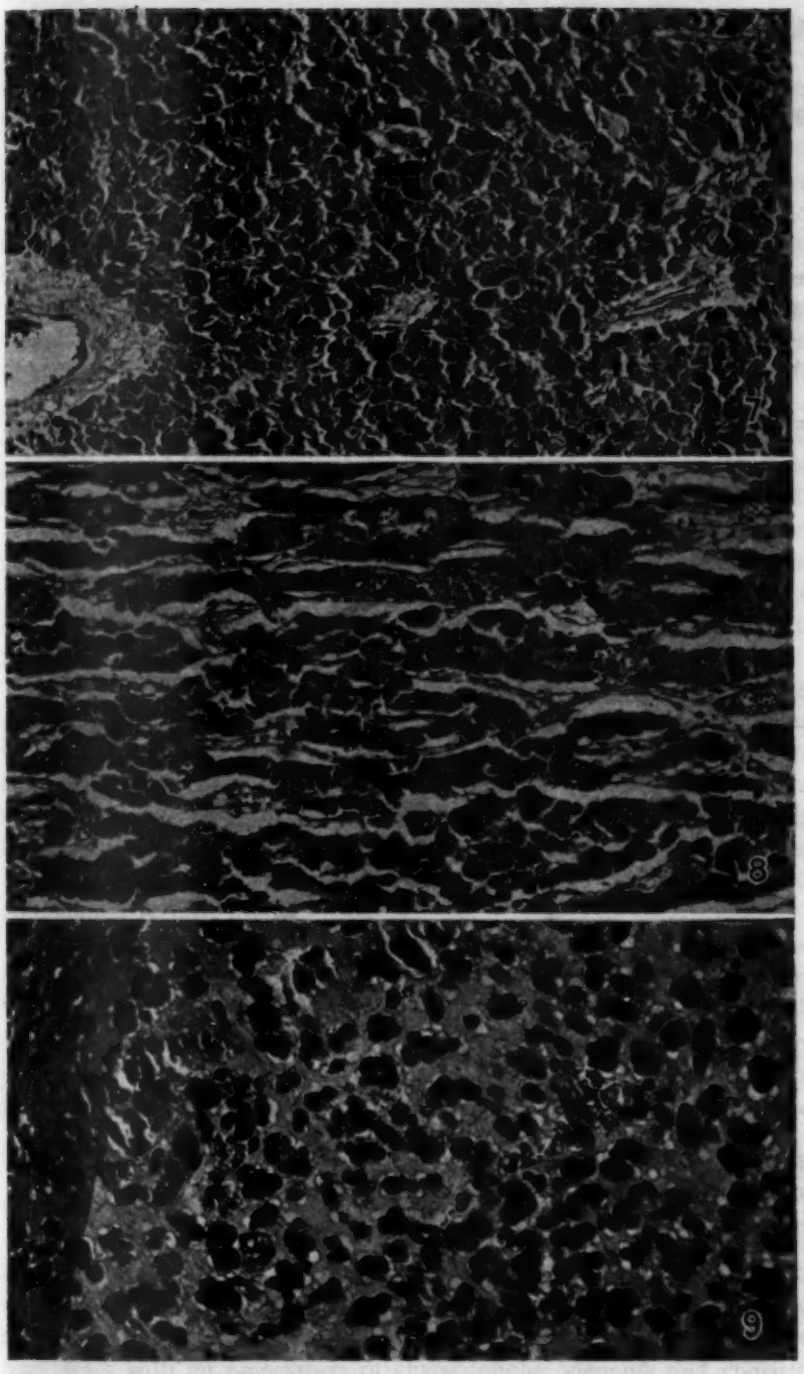


Fig. 7.—Megalocytic adenoma in which the capillaries form a homogeneous network; hematoxylin and eosin; × 50.

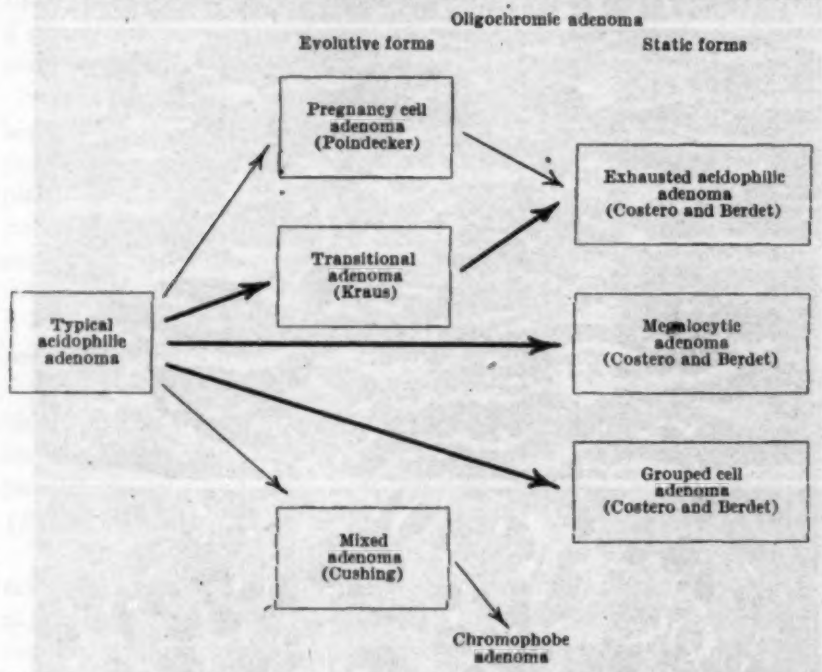
Fig. 8.—Megalocytic adenoma in which the capillaries are parallel; hematoxylin and eosin; × 50.

Fig. 9.—Grouped cell adenoma; hematoxylin and eosin; × 100.

Table 2 shows graphically the probable relationship between the different morphologic varieties of oligochromic adenoma.

Finally, I should like to touch briefly the theme of clinicopathologic correlations. The exhausted acidophilic adenoma is regularly found in a patient with frustrated acromegaly; it does not present any sign of intrinsic malignancy. The most common feature of megalocytic adenoma is the replacing of an acromegaloid syndrome by the syndrome of an intracranial tumor with slow but progressive growth, causing ocular

TABLE 2.—*Probable Relations Among the Outstanding Morphologic Varieties of the Oligochromic Adenoma*



disturbances, diencephalic symptoms and signs of intracranial hypertension. The clinical behavior of grouped cell adenoma is like that of chromophobe adenoma.

POLYMORPHISM OF THE CHROMOPHOBE ADENOMA (ADENOEPITHELIOMA)

The chromophobe adenoma must be considered, in spite of its wide polymorphism, as one sole variety of tumor. The constituent cells show an extensive variety of shapes; the starting point of these variations seems to be in the columnar cells, which mimic the lining cells of the pituitary vesicle. Passing sometimes through an intermediate

stage which resembles the chromophobe cells, they end by forming dense masses closely similar to cords of stratified squamous epithelium. This is why Río Hortega [9a] has classified these tumors as adenoepithelioma.

The following graphic exposition of the main morphologic varieties of adenoepithelioma has been arranged in accord with the degree of evolution of the neoplastic cells.

The section reproduced in figure 10 belongs to an adenoepithelioma of columnar cells similar to those of the pituitary vesicle but arranged in irregular series instead of cavities; the tumor is so fragile that the entire parenchyma appears infiltrated with hemorrhages.

In the adenoepithelioma shown in figure 11, the cells are also columnar in shape, but they are disposed in very dense cords; the fetal character of these cells has already been recognized by Kraus.[6]

It may happen that the columnar cells of the tumor become arranged similarly to glandular ducts, as illustrated in figure 12, which represents an evolution more advanced toward nonspecific differentiation; i. e., the structures reproduced in this tumor are not at all similar to those of the functional portion of the normal hypophysis.

Compare that picture with the one shown in figure 13, another adenoepithelioma of glandular aspect, in which many of the tubular formations have already become transformed into solid trabeculae. The columnar form of the cells has given place to a cuboidal or polyhedral one, and many parts of the tumor resemble the pars distalis of the normal hypophysis. This picture would correspond to a transitional stage between the columnar cell adenoepithelioma and the adenoepithelioma formed by chromophobe cells.

The genetic relationship between the embryonic columnar cells and the chromophobe cells of pituitary tumors must be so close that even in the typical chromophobe adenoma, as the one of figure 14, perfectly developed series of columnar cells may be found; the pseudostratified epithelium with cilia shown in figure 15 was found across the tumoral parenchyma; possibly it may have been lining a cavity which was invaded by the adenoma and caused to disintegrate.

The differentiation of the columnar epithelium may be as pronounced as in the case of a cyst included in another chromophobe adenoma (fig. 16), in which there were not only cilia but also mucinous cells among the epithelium; a connective membrane has developed, which contains tubular glands. All these structures together form a picture similar to the mucosa of the higher respiratory pathways. One therefore deals with an association of chromophobe adenoma and choristoblastic formations of teratoid type.

9. del Río Hortega, A. P.: (*a*) An. Casa de Salud Valdecilla **5**:3, 1934; (*b*) Monograph, Arch. argent. de neurol., 1941.

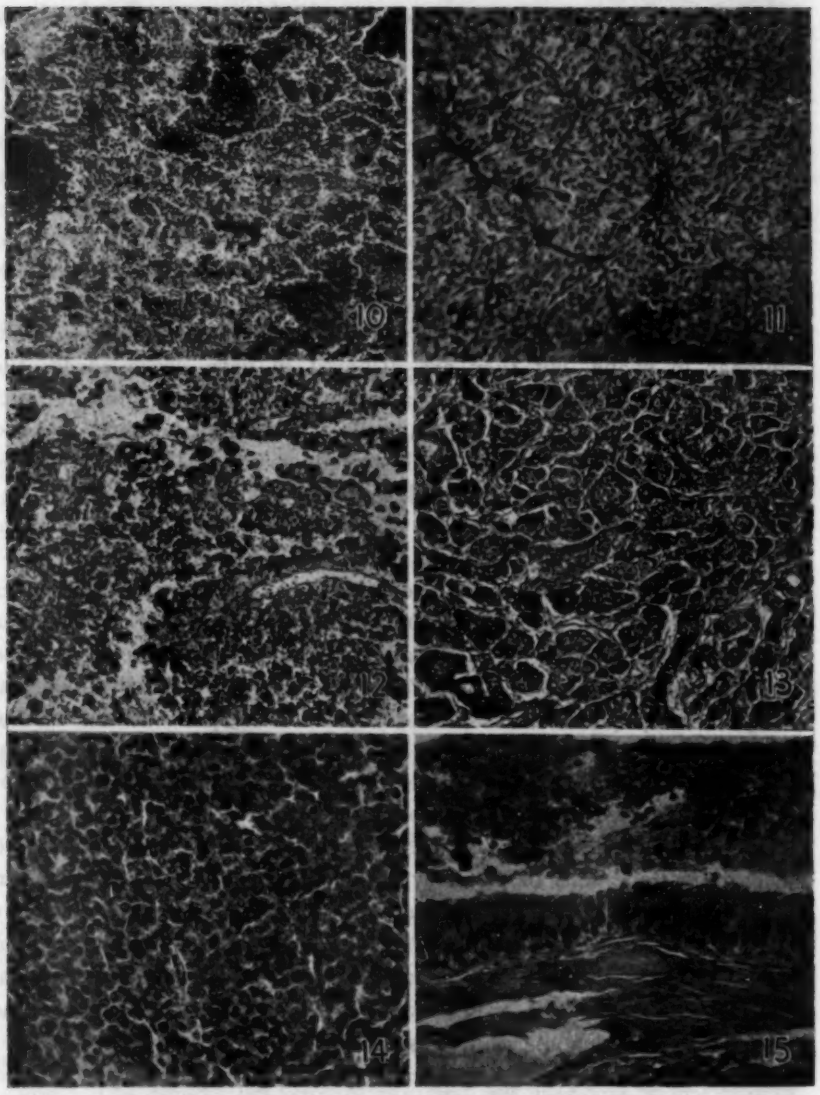


Fig. 10.—Adenoepithelioma with columnar cells; hematoxylin and eosin; × 28.

Fig. 11.—Adenoepithelioma with columnar cells arranged to form dense cords; hematoxylin and eosin; × 71.

Fig. 12.—Adenoepithelioma with columnar cells arranged in such a manner as to resemble glandular ducts; hematoxylin and eosin; × 28.

Fig. 13.—Another adenoepithelioma of glandular aspect; hematoxylin and eosin; × 28.

Fig. 14.—Typical chromophobe adenoma; hematoxylin and eosin; × 99.

Fig. 15.—Pseudostratified epithelium with cilia that may have lined a cavity which was invaded by adenoma and caused to disintegrate; hematoxylin and eosin; × 99.

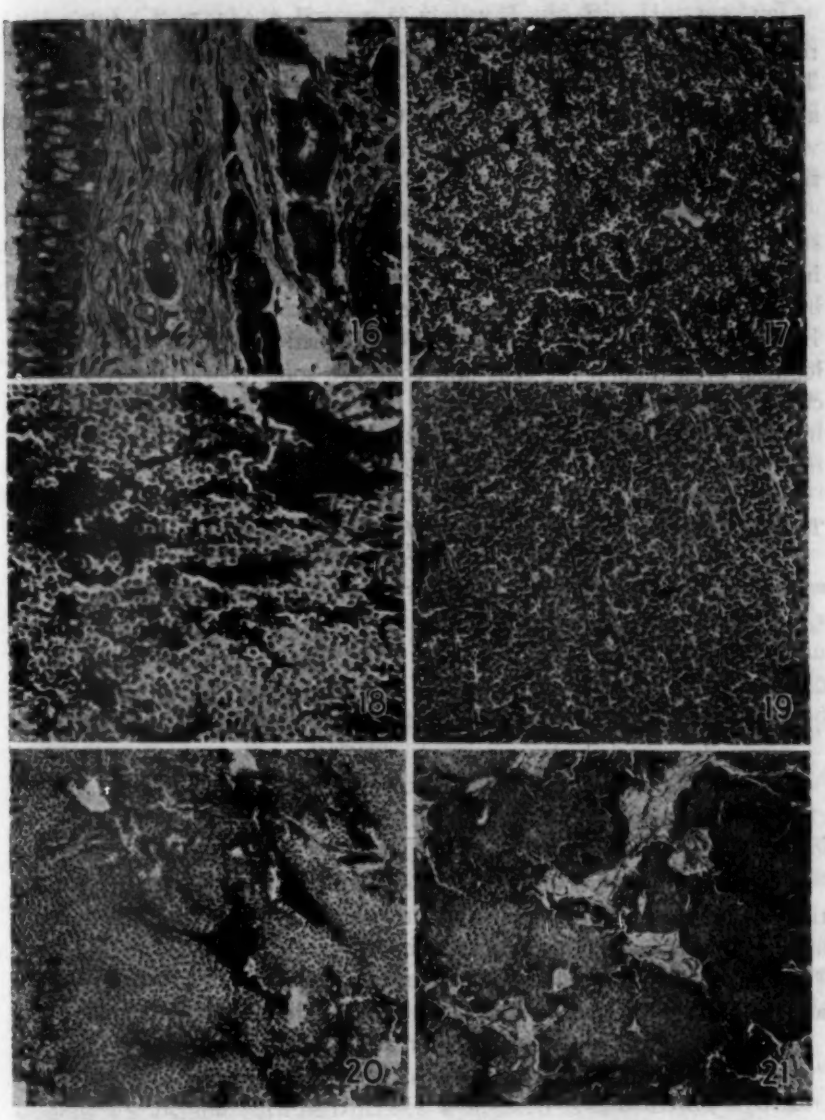


Fig. 16.—Chromophobe adenoma associated with choristoblastic formations of teratoid type; hematoxylin and eosin; × 85.

Fig. 17.—Alveolar adenoma, a variety of chromophobe adenoma; hematoxylin and eosin; × 28.

Fig. 18.—Clear cell adenoma, a variety of chromophobe adenoma; hematoxylin and eosin; × 57.

Fig. 19.—Chromophobe adenoma forming dense epithelial cell cords; hematoxylin and eosin; × 28.

Fig. 20.—Chromophobe adenoma forming anastomosing lobules; hematoxylin and eosin; × 28.

Fig. 21.—Chromophobe adenoma that appears as though formed of independent lobules of squamous epithelium; hematoxylin and eosin; × 28.

The alveolar adenoma, described by Dott and Bailey,[4] is easily recognized by the smallness and the lymphoid aspect of its cells (fig. 17). The clear cell adenoma of Roussy and Oberling[10] (fig. 18) is characterized by the transparency of the cytoplasm. Both tumors are varieties of the chromophobe adenoma and probably represent degenerative phenomena.

The tendency of the chromophobe adenoma to form dense epithelial structures, without glandular character, is illustrated in the three following figures. In figure 19 the neoplastic parenchyma is homogeneous but divided by scarce stroma into dense cell cords of considerable size. In figure 20 these cell cords are well defined and form anastomosing lobules, even though the cells still conserve some characters resembling chromophobe cells. In figure 21 the tumor appears to be formed by independent lobules of squamous epithelium, although there are no intercellular bridges or cornification.

TABLE 3.—*Classification of the Different Morphologic Varieties of Adenoepithelioma According to the Degree of Evolution of Their Cells*

Adeno-epithelioma (chromophobe adenoma)	With columnar cells	Loose
		Dense fetal cell adenoma, Kraus
		Tubular
	With chromophobe cells	Tubular
		With inclusions of columnar epithelium
		Degenerative forms (alveolar adenoma, Dott and Bailey; clear cell adenoma, Roussy and Oberling)
	With polyhedral cells	Cells grouped in cords
		Cells grouped in anastomosing lobules
		Cells grouped in independent lobules

Malignant chromophobe adenoma which is capable of destructive growth and of metastasizing into the lymph glands is rare; there are only 2 cases in our series. The cancerous character is apparent (more than in the cellular variety) in the frequency of mitotic divisions and in the ample zones of necrosis developed in the tumor.

The data exposed in this chapter are summarized in table 3.

SOLITARY SUPRASELLAR CYST (ARCHEOBLASTOMA)

The pituitary vesicle of the embryo, detached from the primitive oral cavity, may persist either totally or partially in the adult person, thus constituting an intracranial cyst situated in the region of the sella turcica. Tumors of this type have been studied by many authors, among them Langer,[11] Tannenheim,[12] Learmonth and Kernohan,[13]

10. Roussy, G., and Oberling, C.: Presse méd. **92**:1799, 1933.
11. Langer, F.: Ztschr. f. Heilk. **13**:57, 1892.
12. Tannenheim, O.: Wien. klin. Wchnschr. 1897.
13. Learmonth, J. R., and Kernohan, J. W.: S. Clin. North America **11**:835, 1913.

Divry and Christophe,[14] Vampre,[15] Bailey[16] and Río Hortega.[9] The solitary suprasellar cyst is variable in size; it contains a fluid in which float abundant cholesterol crystals, often of a greenish color owing to the presence of hematic pigment; the cavity is always lined by cornified squamous epithelium.

The cornification of the lining of the cyst does not happen according to the ordinary manner but follows a peculiar morphologic process, which has been studied by Bailey[17]; Costero and Berdet[9b] have added a few data to this description. A portion of cornified cells is detached and falls into the fluid of the cyst; the vast majority of them, however, are displaced into the connective tissue which surrounds the epithelium; there they provoke the appearance of foreign body giant cells. Later, the cornified masses become calcified, sometimes without losing their histologic arrangement; the giant cells canalize the calcified masses; through the newly formed channels vascular buds penetrate, and finally the cornified layer, embedded in the connective tissue, is completely substituted by bony trabeculae. The following pictures illustrate the different phases of this remarkable process.

In figure 22 one sees a part of the squamous epithelium which lines the wall of a suprasellar cyst. The greater part of the cornified cells form clumps situated toward the cavity; but some cells, marked by an arrow, are clumped together in the basal part of the epithelium next to the connective tissue membrane; this membrane shows a dense lymphoid cell infiltration.

Figure 23 shows at higher magnification the aspect of the masses of cornified cells which are displaced into the connective tissue and surrounded by foreign body giant cells. Note the characteristic stratified disposition of the stratum corneum and the partial conservation of its cellular structures.

A more advanced stage is reproduced in figure 24; the cornified masses, still showing remains of the structures mentioned before, appear in an advanced stage of calcification; close to them there is incompletely formed bony tissue.

Figure 25 derives its interest from the fact that it shows in miscellaneous disposition cornified masses with their characteristic structure, others in different periods of calcification, and bony trabeculae completely formed.

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14. Divry, P., and Christophe, L.: J. de neurol. et de psychiat. **30**:520, 1930.

15. Vampre, E.: Bol. Soc. de med. e cir. São Paulo **14**:149, 1930.

16. Bailey, P., in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, p. 1131; Intracranial Tumors, Springfield, Ill., Charles C Thomas, Publisher, 1933.

17. Bailey, P.: Ann. Surg. **74**:501, 1921.

The solitary suprasellar cyst is always an intrinsically benign formation, but its lining epithelium may show signs of proliferation, especially in the form of budding with dense periphery and loose center, in a manner similar to that of the adamantinoma. Even when the cyst is of great size, it may be well tolerated and the patient may not show important signs of intracranial hypertension. This is explained by the fact that the cyst begins its formation in an early period of the embryonal development, growing simultaneously with the brain and the other parts of the skull, so that the phenomena produced are those of adjustment and not those of compression. As the pituitary vesicle becomes a nonfunctional cyst, the complete or almost complete lack of pars glandularis is frequently manifested in the form of Fröhlich's syndrome. Basing their decision on this sequence of events and on the clinical frequency of these tumors, Costero and Berdet [8b] have separated the solitary suprasellar cyst from the craniopharyngioma, giving to it the name "archeoblastoma."

LIMITATION OF THE CONCEPTS OF ADAMANTINOMA AND TERATOMA

The atypical potentialities of the columnar epithelium lining the wall of the embryonal pituitary vesicle are already manifest in the normal hypophysis. More than a third of normal persons have squamous epithelium in the hypophysis (Erdheim [18]; Simonds [19]; Kiyono [20]; Pérez Lista [21]; Susman [22]). It is possible to find columnar epithelium with goblet cells (Peremeschko [23]; Bryant [24]; Guizzetti [25]; Kiyono [20]; Rasmussen [26a, b]) or tubular glands (Erdheim [18]; Bevacqua [27]; Guizzetti [25]; Lewis and Lee [28]; Rasmussen [26c]; Thom [29]). This means that one must be careful in interpreting the complex tumors derived from the epithelium of the pituitary vesicle, since it is so highly multipotent.

For example, the squamous epithelium of some normal glands and that appearing in archeoblastoma, epithelioma and carcinoma of the pituitary area often show a loose central portion and a dense periphery, as do the enamel germs. I feel that this feature alone is not sufficient

18. Erdheim, J.: Ztschr. f. Path. **4**:215, 1910.
19. Simonds, J. P.: Endocrinology **50**:766, 1922.
20. Kiyono, H.: Virchows Arch. f. path. Anat. **259**:252, 1926.
21. Pérez Lista, M.: Bol. Soc. españ. de biol. 1931.
22. Susman, W.: Brit. J. Surg. **19**:571, 1932.
23. Peremeschko, W.: Virchows Arch. f. path. Anat. **38**:329, 1867.
24. Bryant, W. S.: Anat. Rec. **11**:25, 1916.
25. Guizzetti, P.: Sperimentale, Arch. di biol. **79**:73, 1925.
26. Rasmussen, A. T.: (*a*) Endocrinology **12**:129, 1928; (*b*) Anat. Rec. **41**:273, 1929; (*c*) **55**:139, 1933.
27. Bevacqua, A.: Anat. Anz. **38**:3, 1911.
28. Lewis, D., and Lee, F. C.: Bull. Johns Hopkins Hosp. **41**:241, 1927.
29. Thom, W.: Arch. f. mikr. Anat. **57**:632, 1931.

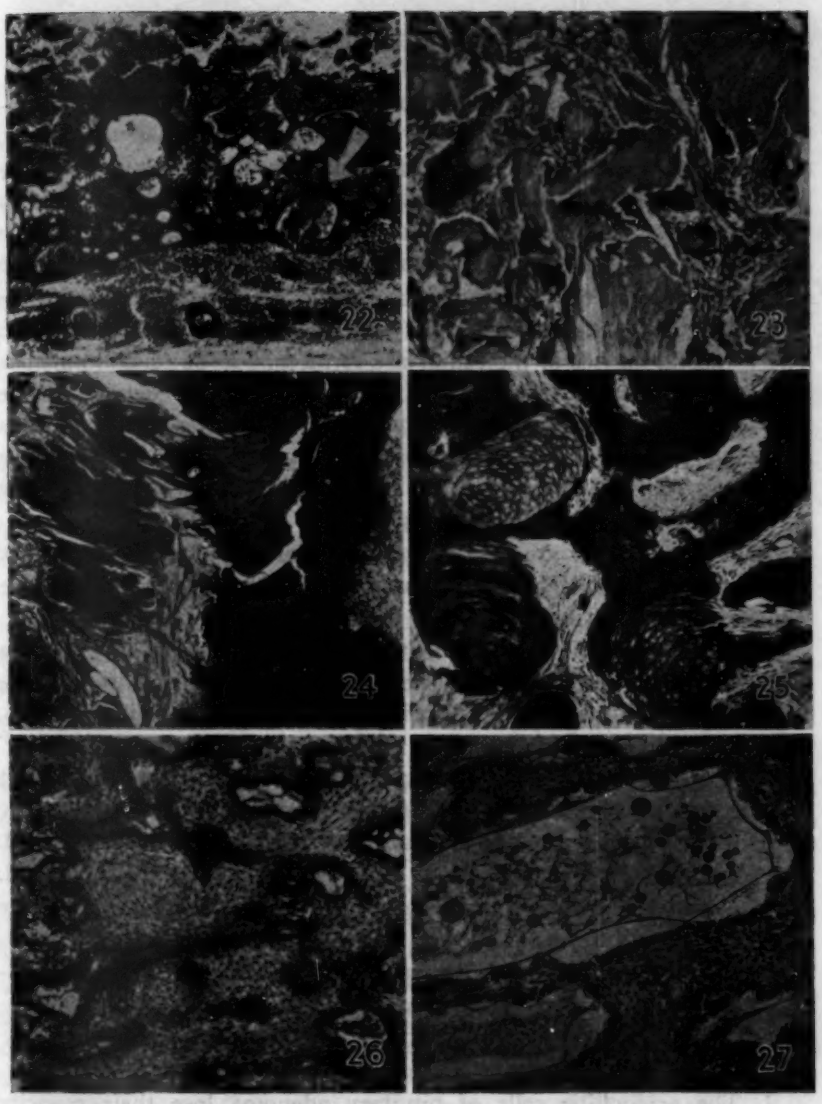

Fig. 22.—A part of the squamous epithelium which lines the wall of a suprasellar cyst (archeoblastoma). Some of the cells (marked by an arrow) are clumped in the basal part of the epithelium next to the connective tissue membrane. This membrane shows lymphoid cell infiltration; hematoxylin and eosin; × 28.

Fig. 23.—Higher magnification of the cornified cells that have been displaced into the connective tissue and surrounded by giant cells; hematoxylin and eosin; × 57.

Fig. 24.—A more advanced stage of the process illustrated in figures 22 and 23; hematoxylin and eosin; × 28. The cornified masses, still showing cellular structures, have undergone calcification. Close to them is incompletely formed bony tissue.

Fig. 25.—A miscellaneous disposition of some cornified masses with their characteristic structures, others in different periods of calcification, and bony trabeculae completely formed; hematoxylin and eosin; × 28.

Fig. 26.—Authentic adamantinoma; hematoxylin and eosin; × 28. Note the interepithelial spaces where the characteristic hyaline ribbons may be seen, some undergoing calcification. They represent the specific secreting activity of the columnar cells and thus manifest the ameloblastic character of these cells.

Fig. 27.—Adamantinoma. It can be identified by the hyaline ribbons and clumps undergoing calcification; hematoxylin and eosin; × 57.

for classifying the tumor as an adamantinoma. In my opinion, adamantinoma is an epithelial tumor whose peripheral cells, densely arranged, are columnar in shape and secrete a calcifiable albuminous mass. The loose central parts of the epithelial cords of the tumor, to which so many investigators have given attention, may also exist in a simple epithelioma or be missing in an adamantinoma, without giving a clue to the diagnosis.

In figure 26, for example, an authentic adamantinoma is shown. The epithelial masses of the tumor are formed by loose central portions and dense peripheral portions; but the most important detail is to be found in the interepithelial spaces, where characteristic hyaline ribbons are seen, some of them undergoing calcification; they represent the specific secreting activity of the columnar cells, thus manifesting the ameloblastic character of these cells.

In figure 27 there are no loose portions, but the ameloblastic nature of the tumor is made sufficiently apparent by the presence of hyaline ribbons and clumps in the process of calcification.

A similar limitation applies to the pituitary teratoma. Under this heading tumors have been described which are really chromophobe adenoma with choristoblastic inclusions, as the one shown in figure 16, or else ossifying archeoblastoma. I believe that the name "teratoma" should be reserved for those organoid tumors constituted by adult tissues, which are formed from at least two different blastodermic layers; this happens when such tissues exert reciprocal inductions and, therefore, grow synergically. If, as often happens in the pituitary gland, the tumor seems to be derived from a single anlage with multiple potentialities of differentiation, one of which has preponderant development, one is dealing with a hamartoma, using the adequate nomenclature of Albrecht, and not with a true teratoma.

CONCLUSIONS

1. The acidophilic cells of pituitary adenoma lose their capacity for elaborating specific granulations with relative frequency; in this way oligochromic adenoma arises. These tumors tend to adopt one of the following three forms: (1) The tumor cells become spheroid, their nuclei are eccentric in position and lobulated in shape, and they secrete a very fluid albuminous substance, which is deposited in the stroma (exhausted acidophilic adenoma); (2) the tumor cells double their size, show an eccentric nucleus and are arranged in anastomosing cords (megalocytic adenoma); (3) the tumor elaborates an abundant quantity of colloid substance in which the cells are deposited, forming "isogenic groups" (grouped cell adenoma).

2. Between the typical acidophilic adenoma and the exhausted one, different transitional types are found. The megalocytic adenoma probably represents a frustrated form of acidophilic adenoma. Grouped cell adenoma may be interpreted as a degenerated form of acidophilic adenoma.

3. The polymorphism of the adenoepithelioma of the pituitary gland is a consequence of the multipotentiality of the embryonic epithelium lining the pituitary vesicle. The less differentiated tumors are formed by columnar cells arranged in rows; the most differentiated ones, by polyhedral cells grouped in cords. The chromophobe adenoma represents an intermediate stage between the two extremes.

4. The name "archeoblastoma" has been proposed for the solitary suprasellar cyst, which is limited by a cornified squamous epithelium and contains an aqueous fluid rich in cholesterol crystals and blood pigments. This cyst is a choristoblastic formation which represents persistence of the pituitary vesicle of the embryo in the adult. The most characteristic morphologic feature of the structure of archeoblastoma is the existence of cornified masses embedded in the connective tissue; these masses are first calcified and finally transformed into bony laminas; this is a rare case of ossification arising on epithetlial tissue.

5. Only those epithelial tumors which show a capacity for elaborating calcifiable hyaline substance should be considered as adamantinoma. True adamantinoma of the pituitary gland is frequent.

6. The tumors formed from miscellaneous structures derived from a unique and multipotent embryonal anlage are not to be considered as true teratomas. These false teratomas, which are recognizable through the observation that the development of one structure is predominant in comparison with the rest, should be classified under the classic nomenclature of Albrecht as hamartoma when the neoplastic structures belong to the tissue of the normal organ and as choristoma when the tumoral components are foreign to the organ in which they develop. True teratoma of the pituitary gland is rare.

EFFECT OF SODIUM CHLORIDE DEPRIVATION ON THE GROWING RAT

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DURHAM, N. C.

SODIUM and chloride deficiency in experimental animals has received only slight attention. In 1937 Orent-Keiles, Robinson and McCollum [1] reported the gross changes occurring in a group of rats which had been fed a diet deficient in sodium and chloride as a control for their study of sodium deprivation. These changes consisted of bleeding from the mouth, ears, nose and forepaws and passage of dark red urine. At autopsy these rats had hemorrhages in the liver, and the adrenal glands were small but grossly normal. Histologic examination was not reported.

In contrast with the paucity of reports on combined sodium and chloride deficiencies, single element studies on the influence of sodium deprivation and chloride deprivation have been relatively numerous.

For many years sodium deprivation has been known to affect unfavorably both growth and the utilization of nutritive elements.[2] In addition, sodium lack has been shown by Orent-Keiles, Robinson and McCollum [1] to produce ulceration and keratinization of the cornea, with the formation of an exudate. In addition, a pronounced loss of hair of the eyelids has been recorded. These changes did not respond to administration of carotene. In a subsequent publication Follis, Orent-Keiles and McCollum [3] described the mechanism of the ocular change as a caking of the exudate on the lids producing obstruction of the ducts of the meibomian glands. This was followed by metaplasia of the columnar and goblet cells producing keratinization. That injury of cells had been produced was indicated by the fact that the zone was

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From the Department of Pathology, Duke University School of Medecine.

1. Orent-Keiles, E.; Robinson, A., and McCollum, E. V.: Am. J. Physiol. **119**:651, 1937.

2. (*a*) Kahlenberg, O. J.; Black, A., and Forbes, E. B.: J. Nutrition **13**:97, 1937. (*b*) Marquis, M.: Compt. rend. Soc. de biol. **128**:449, 1938. (*c*) Orent-Keiles and co-workers.[1]

3. Follis, R. H.; Orent-Keiles, E., and McCollum, E. V.: Arch. Path. **33**:504, 1942.

infiltrated by polymorphonuclear leukocytes. Retardation of growth of bone and atrophic testicular changes were ascribed to inanition.

In 1942 Voris and Thacker [4] concluded that the substitution of bicarbonate for chloride in the diet of growing rats was followed by depression of appetite, increased consumption of water, retardation of growth, smaller gain of fat and water with larger proportionate gains of protein and residual organic substance, slight decrease of fecal nitrogen and slight increase of energy utilization with heat production. Greenberg and Cuthbertson [5] failed to confirm the loss of appetite; they found that the chloride-deficient rats ate more, though they gained less. They found in addition that, as would be expected, the blood chloride was diminished, the carbon dioxide–combining power was increased, and chloride retention occurred within a few hours. Later they [6] described cystlike changes of the glomeruli and degenerative lesions of the tubules with homogeneous masses in the lumens. Some tubules showed scarring. These changes were ascribed to "overwork of the kidneys in conserving chloride." Lowenhaupt and Greenberg [7] carried the study further and concluded that calcium was precipitated in the lumens of collecting tubules, with consequent blocking of the tubules and the production of hydronephrosis and a granulomatous reaction in association with foreign material.

Our interest in sodium chloride deficiency has arisen out of a projected study of heat stroke. Inasmuch as heat stroke is considered a hemorrhagic disease based on increased capillary porosity [8] and inasmuch as hemorrhagic tendencies have been reported in rats deficient in sodium chloride,[1] it seemed likely that if a condition analogous to heat stroke could be produced in rats, it would be facilitated by a dietary sodium and chloride deficiency. Consequently, a pilot experiment was undertaken, in which sodium and chloride deficiency was studied. Our results are at such variance with the findings of others that a separate report of this experiment seems warranted.

MATERIALS AND METHODS

Ninety recently weaned white rats weighing between 21.5 and 59.4 Gm., an average of 35.15 Gm., were fed synthetic diets (table) according to the following regimen: Eighteen were fed a control diet; 72, a diet deficient in sodium and chloride. At the end of one month the test group was divided into three subgroups, and the diets were altered as follows: A group of 24 rats continued to subsist on the sodium and chloride-deficient diet, a group of 24 were fed a sodium-deficient diet—this change being effected by the addition of potassium chloride—and 24 were

4. Voris, L., and Thacker, E. J.: J. Nutrition **23**:365, 1942.
5. Greenberg, D. M., and Cuthbertson, E. M.: J. Biol. Chem. **145**:179, 1942.
6. Cuthbertson, E. M., and Greenberg, D. M.: J. Biol. Chem **160**:83, 1945.
7. Lowenhaupt, E., and Greenberg, D. M.: Arch. Path. **42**:49, 1946.
8. Wright, D. O.; Reppert, L. B., and Cuttino, J. T.: Arch. Int. Med. **77**:27, 1946.

given a chloride-deficient diet—effected by the addition of sodium bicarbonate. These changes of dietary regimen were made in an effort to reproduce the changes described for a single element deficiency. A short time before the end of the experiment 3 rats from the chloride-deficient group and 4 rats from the group deficient in sodium and chloride were transferred to the control diet in order to observe the effect on the growth of the rat following this restoration of sodium chloride. The rats were housed in cages containing groups of 6. Because of a tendency toward cannibalism among rats, it was necessary to drop 41 rats from the experiment to avoid the possibility of error of interpretation from this source. Food was weighed each day to ascertain that adequate intake of food was maintained, and 2 animals were killed at weekly intervals beginning at the fourth week.

GROSS APPEARANCE OF THE ANIMAL

The weight curve showed a distinct retardation of growth in sodium and chloride–deficient animals (fig. 1). On separation into sodium and chloride–deficient,

Formulas of Diets

	Control	Sodium and Chloride–Deficient Diet	Sodium-Deficient Diet	Chloride-Deficient Diet
Sucrose	1,300 Gm.	1,300 Gm.	1,300 Gm.	1,300 Gm.
Casein	400 Gm.	400 Gm.	400 Gm.	400 Gm.
Hydrogenated cottonseed oil ("Crisco")	200 Gm.	200 Gm.	200 Gm.	200 Gm.
Choline di-hydrogen citrate	4 Gm.	4 Gm.	4 Gm.	4 Gm.
Vitamin mixture *	½ unit	½ unit	½ unit	½ unit
Basic salt mixture †	102.5 Gm.	102.5 Gm.	102.5 Gm.	102.5 Gm.
Sodium chloride	20 Gm.	.....	.....	.....
Potassium chloride	.....	.....	15 Gm.	.....
Sodium bicarbonate	.....	.....	.....	34 Gm.

* The vitamin mixture was made up of: peroomorph liver oil, 4 Gm.; thiamine hydrochloride, 10 mg.; riboflavin, 20 mg.; pyridoxine hydrochloride, 10 mg.; calcium pantothenate, 100 mg.; nicotinic acid, 30 mg.; wheat germ oil, 4 mg., and naphthohydroquinone, 50 mg. Note: This formula is considered 1 unit and added to 4 Kg. of diet.

† The basic salt mixture was made up of: $CaCO_3$, 300 Gm.; $K_2CO_3.1½\ H_2O$, 220 Gm.; KH_2PO_4, 340 Gm.; MgO, 40 Gm.; $FeC_6H_5O_7.3H_2O$, 100 Gm.; $CuSO_4$, 20 Gm.; $MnSO_4$, 5 Gm.

chloride-deficient and sodium-deficient groups, the growth curve continued low. The chloride deficient group grew slightly faster than the sodium and chloride–deficient group, and the sodium-deficient group did not grow as fast as the group deficient in sodium and chloride. These findings are in essential agreement with previous observations.[9] When rats previously fed sodium-deficient and sodium and chloride–deficient diets were changed to the control diet, there was rapid acceleration of growth. This agrees with previous observations.[2b] As in previous reports,[10] alterations occurred in the conjunctiva at about the eighth to tenth week. These changes were grossly most numerous in the sodium and chloride–deficient group (40 per cent) and the sodium-deficient group (36.3 per cent), but they also occurred in the chloride-deficient group (12 per cent) and the control (14.3 per cent). There

9. Orent-Keiles and co-workers.[1] Kahlenberg and co-workers.[2a] Marquis,[2b] Follis and co-workers.[3] Voris and Thacker.[4] Greenberg and Cuthbertson.[5]

10. Orent-Keiles and co-workers.[1] Kahlenberg and co-workers.[2a] Marquis.[2b] Follis and co-workers.[3]

was loss of hair on the shoulders and the head in 20 per cent of the sodium and chloride-deficient group and 9 per cent of the sodium-deficient group. This feature was not observed in the control or in the chloride-deficient group.

MICROSCOPIC OBSERVATIONS

Sections of liver, spleen, pancreas, kidney, skin, stomach, intestine, lung, heart, thyroid gland and trachea, tongue, eye, brain, bone, testicle and adrenal gland were routinely examined. Hematoxylin and eosin preparations were used routinely and special technics as required, such as von Kossa stains for calcium identification.

Sodium-Deficient Group.—Atrophy of the epithelium of the conjunctiva and meibomian ducts was observed in 25 per cent of the 12 animals of this group which were considered valid for the experiment. Polymorphonuclear leukocytes were observed infiltrating the conjunctivas in only 16.6 per cent of these animals (fig. 2). This reaction is similar to that described by Orent-Keiles and co-workers [1] and Follis and co-workers.[3] However, in this series it is to be pointed out that this

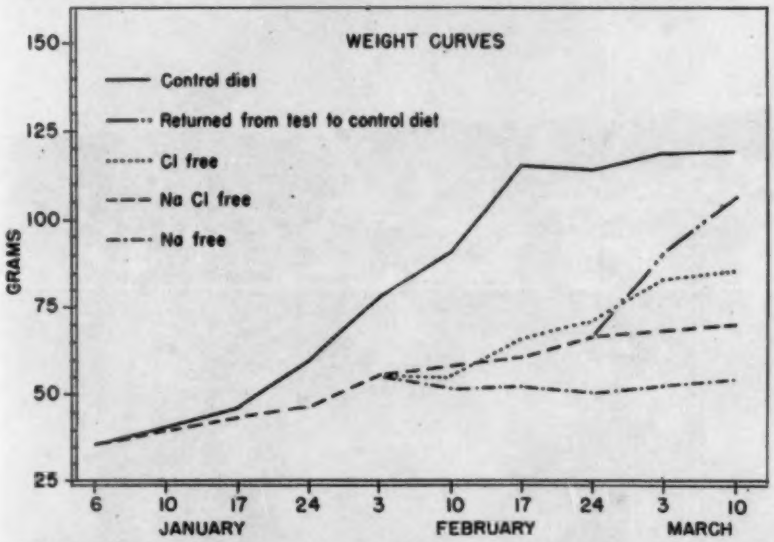

Fig. 1.—Weight curves showing retardation of growth observed as a result of variation in diet; a marked acceleration of weight gain is noted in the group of rats returned from a test diet to the control diet.

reaction was not specific and was found in all categories of animals. Deposition of calcium was noted in the muscle in 16.6 per cent and in the brain in 8.3 per cent (fig. 3 *A*). In both the muscle and the brain the initial injury was focal necrosis with calcification and cellular reaction in the form of lymphocytic infiltration and macrophagic proliferation. These lesions were also surrounded by glial (astrocytic) proliferation. Two of the animals had pneumonic consolidation and renal hemorrhage with dilatation of the renal tubules. The bones uniformly showed retardation of growth at the epiphysial line.

Chloride-Deficient Group.—Calcium deposition similar to that described by Lowenhaupt and Greenberg [7] was observed in the tubular epithelium of the kidney in 12.5 per cent of the 8 animals of this group which were considered valid (fig.

3 *B* and *C*). However, this same process was found in 23.6 per cent of the sodium and chloride–deficient animals and 14.3 per cent of the control animals. However, mononuclear cell infiltration of the interstitial tissues of the kidneys was found in 37.5 per cent. This type of lesion was found in only 1 other animal, and this

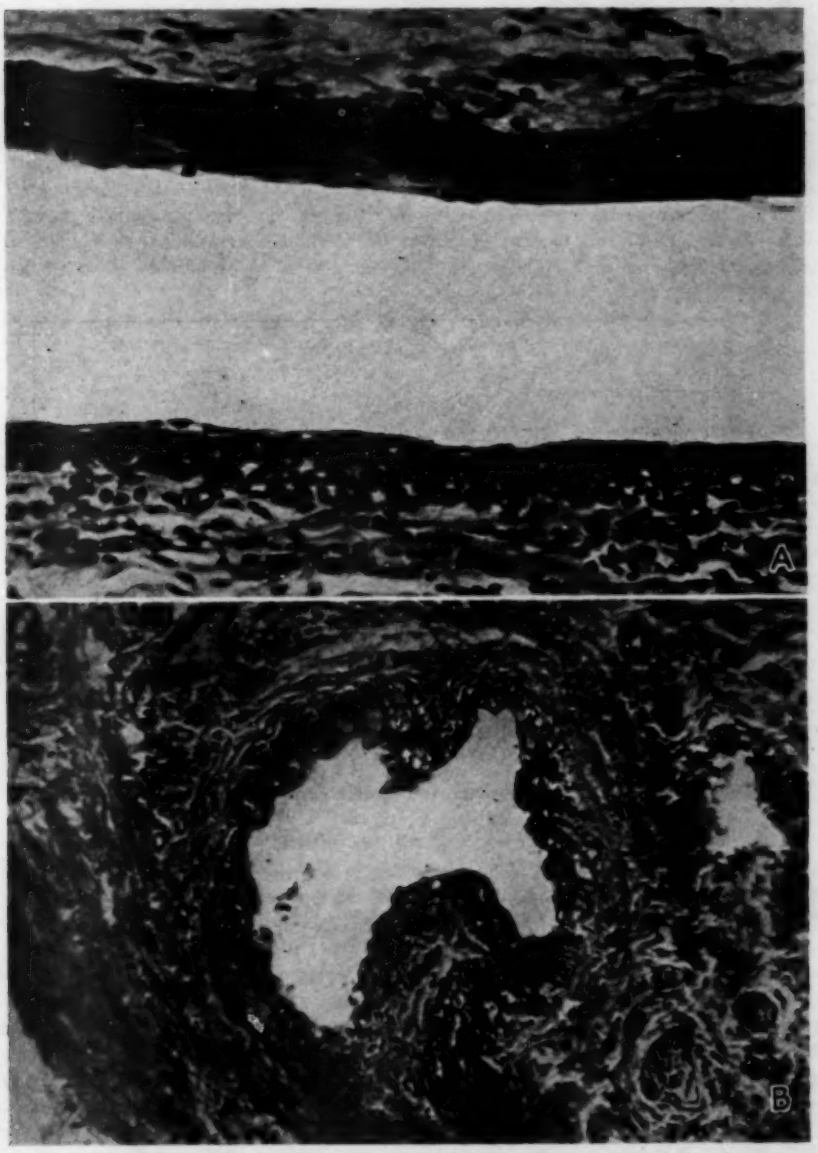

Fig. 2.—*A*, atrophy and inflammation of the conjunctival sac, found in sodium-deficient and sodium and chloride–deficient rats and, less frequently, in chloride-deficient rats. Hematoxylin and eosin; × 350. *B*, atrophy and inflammation of lacrimal ducts. Hematoxylin and eosin; × 150.

animal belonged to the sodium and chloride-deficient group. We were unable to confirm the report of dilatation of tubules and hydronephrosis observed in connection with this type of lesion. The focal necrosis with deposition of calcium was found in the brain in 12.5 per cent of this test group. There was atrophic change

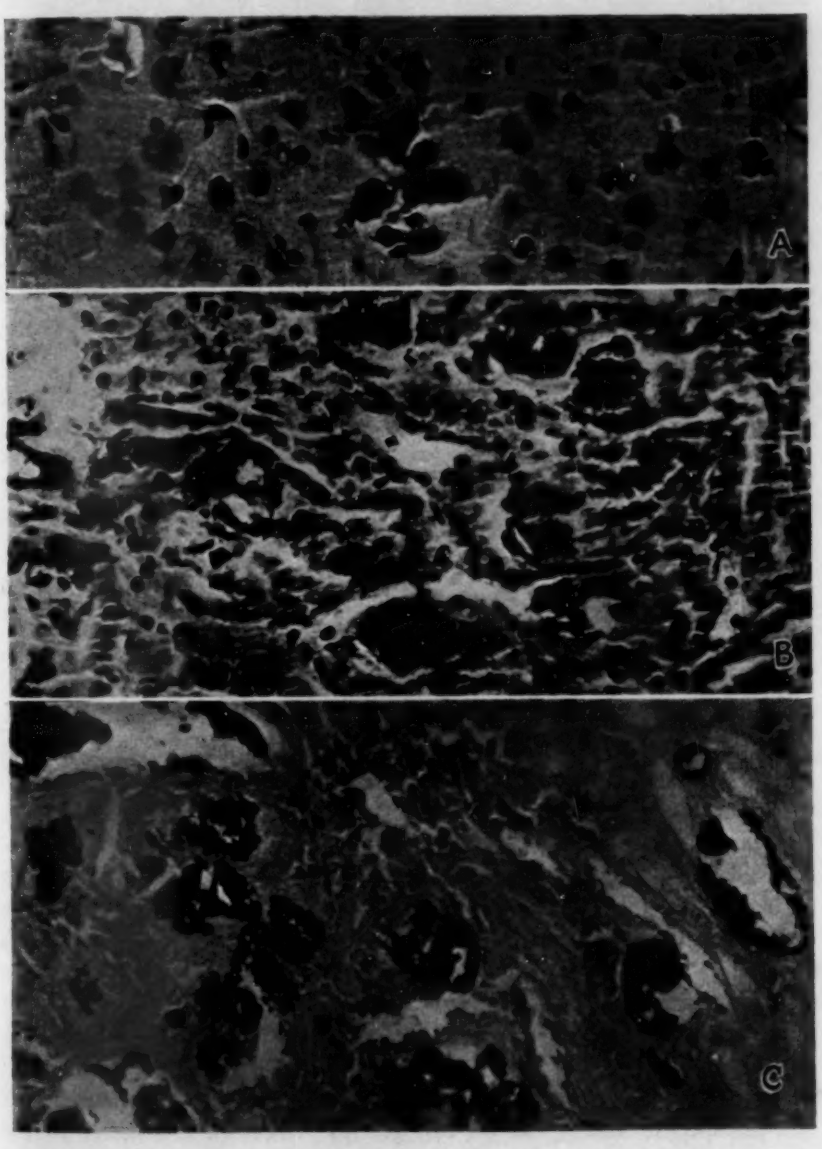

Fig. 3.—*A*, calcium deposited in the brain, in an area of gliosis; the specificity of this lesion is not apparent, but it occurs in greatest frequency in the chloride-deficient and sodium and chloride-deficient groups. Hematoxylin and eosin; × 350. *B*, calcium deposition in renal tubules. No dilatation of tubules was found. Hematoxylin and eosin; × 350. *C*, another view of calcification of renal tubules. Von Kossa stain; × 350.

of the conjunctiva with cellular infiltration in 18.1 per cent and atrophy of the lingual epithelium in 39.5 per cent. One instance each of edema of the lung, hemorrhage of the kidney and necrosis of the liver was observed.

Sodium and Chloride–Deficient Group.—Atrophy of the conjunctival epithelium similar to that found in sodium deficiency was observed in 64.7 per cent of the 17 animals of this group which were considered valid. There was cellular infiltration, chiefly of polymorphonuclear leukocytes, in the conjuctiva and subconjunctiva in 53 per cent. There was atrophy of the skin in 20 per cent and atrophy of the tongue in 10 per cent. Atrophy of the testicular epithelium was observed in 15 per cent. Calcium deposition was found in the renal tubular epithelium in 23.6 per cent and in the brain in 10 per cent. Pneumonic consolidation was found in 33 per cent and pulmonary hemorrhage in 5 per cent.

Animals Returned to Control Diet.—The animals returned from test diets to the control diet showed accentuation of the lesions as indicated by frequency of occurrence. Of the 3 rats from the chloride-deficient group fed the control diet, 2 had calcium deposits in the renal tubular epithelium and also the focal lesion with calcification in the brain. One showed atrophy of the conjunctiva, with polymorphonuclear leukocytes infiltrating the stratified squamous epithelium and subepithelial tissues. Of the 4 rats returned to the control diet from the sodium and chloride–deficient diet, all 4 showed atrophy of the conjunctiva, and 2 had polymorphonuclear leukocytes infiltrating the tissues. Three of the 4 rats showed degenerative changes in the voluntary muscles with macrophagic response and calcification and calcium deposition in the renal tubular epithelium. There was 1 instance each of calcium deposition of the cerebral cortex, atrophy of the skin and atrophy of the testis.

COMMENT

In analyzing the results of our experiment we have been able to recognize the lesions described in single element deficiencies. However, we have been unable to attain any degree of specificity in the production of the lesions. The ocular changes described in connection with sodium deficiency have been produced in our experiment in all types of deficiency. The animals deficient in sodium and chloride are even more prone to show these changes than are the sodium-deficient animals. The hypothesis advanced by Follis,[11] that the ocular changes in sodium-deficient rats might be explained on the basis of the production of electrolyte-reduced tears with consequent lowering of concentration to the point of isotonicity or even hypotonicity, a state producing irritation of the conjunctival epithelium, which is conditioned to hypertonicity, seems to us equally applicable to sodium and chloride deficiency, as well as to chloride deficiency. On the other hand, it might also be postulated that a deficiency of electrolytes diminishes the secretion of tears, producing irritation by simple drying.

The deposition of calcium in the renal tubules was an inconsistent and nonspecific findings in all test groups. In only 1 instance in the whole of the experiment were we able to demonstrate the dilatation of the tubules described in chloride deficiency. The pathogenesis of the

11. Follis, R. H.: The Pathology of Nutritional Disease, Springfield, Ill., Charles C Thomas, Publisher, 1948.

deposition of the calcium of the tubules may well be explained by the mechanism proposed by Lowenhaupt and Greenberg; that is, owing to the alkalinity of the urine with possible elevation of phosphate concentration in convoluted and collecting tubules, the tubular epithelium is damaged and favorable circumstances are provided for the precipitation of calcium salt. However, we were not able to confirm the finding that this precipitation produced an obstruction of the lumens of these tubules with consequent development of hydronephrosis, since in only 1 animal were we able to make such an observation. The significance of this observation therefore seems entirely compatible with the finding of nonspecificity of this lesion, in that one might expect to find this type of alteration in any of the deficiencies studied by us. In addition to the deposition of calcium salt in the tubules of the kidney, we were able to find deposition of this salt in muscles and brain. In the brain the lesion consisted of deposition of calcium salt about damaged nerve cells of the cortex as indicated by von Kossa's stain, and with this injury there appeared a reaction in the form of gliosis. These lesions were found in greater numbers among the chloride-deficient animals, but the observation could be made in all of the test animals, with the least consistent findings being recorded for the sodium and chloride–deficient group. Other pathologic conditions, such as atrophy of the tongue, edema of the lungs, necrosis of the liver, and pneumonia with abscess formation, were found without regard to specificity in the test groups and without sufficient consistency to warrant interpretation.

We were unable to find any evidence of hemorrhagic tendencies in any of these groups, including the group fed the diet deficient in sodium and chloride. It might be that the discoloration observed by Orent-Keiles, Robinson and McCollum was due to production of porphyrin and not to blood.

SUMMARY

Sodium and chloride, chloride, and sodium deficiencies were studied in colonies of growing rats by means of synthetic diets.

We have been unable to determine or recognize hemorrhagic tendencies in any of these deficiencies.

Changes in the conjunctiva and meibomian ducts similar to those described for sodium deficiency were found in the animals of this experiment. We were unable to find a specificity for this lesion since it was observed with equal frequency in the sodium and chloride–deficient group and the sodium-deficient group, and was noted in 3 rats of the chloride-deficient group.

Calcium deposition in the renal tubules similar to that described in connection with chlorine deficiency was found in these test groups, but without consistency or specificity. We were unable to confirm the findings of hydronephrosis.

General Reviews

INTERRELATIONSHIP OF DISEASES OF THE LIVER AND THE BRAIN

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WITH the increasing interest in specialization, more and more research is being focused on diseases of isolated organs. As a result of this trend it is frequently forgotten that there is often an interrelationship between the diseases of the various body structures. One of the most striking and as yet unsolved examples of such associated organic diseases is the combined involvement of the liver and the brain. This unusual association of diseases of separate organs was first described about sixty years ago by Gowers,[1] who observed 2 cases in which acute chorea was associated with cirrhosis of the liver. At autopsy, however, no lesions were observed within the central nervous system. Two years later, in 1890, Ormerod[2] and Homén[3] described in separate publications the appearance of cerebral and hepatic disease as concomitant occurrences. Ormerod reported a single case of acute involvement in which a boy at autopsy had bilateral symmetric softening of the putamen and cirrhosis of the liver. Homén described a unique and unknown chronic familial disease affecting 3 of 11 children and marked by progressive chorea, dementia, and death in three to seven years. All the patients (two brothers and a sister) showed symmetric lenticular lesions and severe cirrhosis of the liver.

In 1912 Wilson,[4] in a masterful publication, described in detail a rare familial disease of the nervous system which he called "progressive lenticular degeneration" and which has since been known as Wilson's disease or, more recently, as hepatolenticular degeneration (Hall[5]). This disease was characterized by the progressive development in young adults of widespread involuntary movements (usually in the nature of

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1. Gowers: A Manual of Diseases of the Nervous System, London, J. & A. Churchill, 1888, vol. 2, p. 656.
2. Ormerod: St. Barth. Hosp. Rep. **26**:57, 1890.
3. Homén, E. A.: Neurol. Centralbl. **9**:514, 1890.
4. Wilson, S. A. K.: Brain **34**:295, 1912.
5. Hall, H. C.: La dégénérescence hepatolenticulaire, Paris, Masson & Cie, 1921.

tremor or chorea), severe rigidity of the musculature, difficulty in articulation and deglutition, and contractures with progressive emaciation. There was also some associated emotionalism, such as spasmodic crying and laughing, and a slight degree of dementia. The course was acute or chronic and invariably terminated fatally. Pathologically, the most striking lesions consisted of bilateral symmetric degeneration of the lenticular and caudate nuclei and cirrhosis of the liver.

The most striking of the clinical features of Wilson's disease are the tremor and the rigidity. The tremor often appears first in the upper limbs and is rhythmic, often wide in range, and severe. It soon spreads to involve all the skeletal musculature, especially the distal groups, but may also implicate the jaw, the head and the neck. Concomitant with, or shortly after, the onset of the tremor the muscular rigidity makes its appearance. The rigidity of the limbs and the face becomes progressive and outstanding. As a result of the muscular stiffness, there is considerable difficulty in maintaining equilibrium. Helplessness becomes more advanced and even profound. Contractures appear at the elbow, the knee and the hip. The facial musculature also becomes rigid and immobile; the corners of the mouth become retracted, and the upper teeth and gums remain visible, producing the appearance of a rather fatuous persistent smile. Saliva often runs from the lips. Dysphagia and dysarthria soon appear. The difficulty of articulation becomes progressive until the patient is unable to speak at all (this adding to his helplessness). The dysphagia produces progressive emaciation, which is a factor in the lethal outcome. At no time do these patients show any true weakness or sensory involvement.

Mental changes are generally more apparent than real. The patient's extreme rigidity, the fixed smile and the dysarthria often produce a false impression of the patient's mental status; however, definite emotional disturbances do occur. There is emotional overaction with involuntary laughing or crying and some narrowing of the mental sphere. As a rule the intellectual faculties are well preserved in spite of the "idiotic" appearance of the patient. Campbell and Morse [6] observed some intellectual impairment in their patients.

Another curious feature of this disease is the occasional presence of a ring of greenish brown pigment on the under surface of the cornea near the limbus. This is known as the Kayser-Fleischer,[7] ring and when present is characteristic of this symptom complex.

Generally the cirrhotic liver produces no clinical disturbances. As a rule, the liver is not palpable and tests of function have proved incon-

6. Campbell, C. M., and Morse, M. E.: J. Neurol. & Psychopath. **5**:28, 1924.

7. Kayser, B.: Klin. Monatsbl. f. Augenh. **40**:22, 1902. Fleischer, B.: Deutsche Ztschr. f. Nervenh. **44**:179, 1912.

clusive with respect to hepatic dysfunction. In 3 of Wilson's cases an attack of jaundice preceded the cerebral symptoms by years. Apparently initial jaundice and even ascites are not uncommon as predecessors of the illness, but actual symptoms of cirrhosis appearing during the progression of the cerebral symptoms are uncommon. As will be shown later, many authors feel that the hepatitis may be fatal before cerebral symptoms appear. Cases have been described in which such isolated hepatic disease has occurred in siblings of patients suffering from typical Wilson's disease.

Clinically, two types of the disease can be recognized, the acute and the chronic. In the acute form there is often a slight elevation of temperature with a fatal outcome in a few months (de Lisi,[8] Howard and Royce [9] and von Dziembowski [10]). In the chronic form the course of the illness may extend over a period of many years (forty-three years, according to Lüthy [11]). Cases have been reported from many parts of the world. There is no sex prevalence.

The pathologic aspects of this disease are also very unusual and characteristic. There is generally bilateral and symmetric involvement of the lenticular nucleus implicating chiefly the putamen and to a lesser extent the globus pallidus, the caudate nucleus and the external capsule. In many cases the involved structures are shrunken and sclerosed, while in other cases these structures show softening necrosis and cavity formation. Histologically, there is a gradual destruction of parenchyma, both cells and processes, with these being gradually replaced by a tremendous glial overgrowth. During the process of degeneration numerous fat granule cells invade the involved areas. The macroglial overgrowth results in the formation of numerous giant glial cells referred to as Alzheimer cells. If the process becomes arrested at this stage, the involved structures appear shrunken. Often, however, the glial overgrowth also undergoes degeneration resulting in the formation of cystic cavities filled with a loose meshwork of glial fibers and remnants of the preceding degenerative process. No inflammatory elements can be seen. Scattered lesions can also be found in other regions of the nervous system, such as the optic thalamus, the cerebral cortex, the red nucleus and the cerebellum. These consist of mild nerve cell changes and some glial reaction (Pollak,[12] Pfeiffer [13] and Howard and Royce [9]). Actually, as one reviews the literature, it becomes more and more apparent that the cerebral lesions are not localized to the lenticular nuclei as emphasized by Wilson, but occur with equal frequency and severity within

8. de Lisi, L.: Riv. di pat. nerv. **34**:1, 1929.
9. Howard, C. P., and Royce, C. E.: Arch. Int. Med. **24**:497, 1919.
10. von Dziembowski, S.: Deutsche Ztschr. f. Nervenh. **57**:295, 1917.
11. Lüthy, F.: Deutsche Ztschr. f. Nervenh. **123**:101, 1932.
12. Pollak, E.: Ztschr. f. d. ges. Neurol. u. Psychiat. **77**:37, 1922.
13. Pfeiffer, J. A. F.: J. Nerv. & Ment. Dis. **65**:289, 1917.

scattered areas of the cerebral cortex and subcortical white matter (Barnes and Hurst,[14] von Braunmühl,[15] Bielschowsky and Hallervorden[16] and Richter[17]). The hemispheric lesions resemble those within the lenticular nucleus and consist of a breakdown of the interstitial tissues with secondary reaction of the neuroglia. In many cases there is a frank, grossly visible necrotizing destruction of the cerebral convolutions, while in others only microscopic changes are seen, consisting chiefly of degeneration of the neurons and glia without neuroglial proliferation or vascular changes (Eicke,[18] Kuiper[19] and Spielmeyer[20]).

The liver always shows an advanced stage of portal cirrhosis. It is generally smaller than normal, firm, hard and nodular. In some nodules scarcely a single normal cell is found, most of the cells being necrotic and shrunken. There is marked proliferation of the portal connective tissue, which is filled with hypertrophying bile ducts.

From the characteristic features of this syndrome it is apparent that the pathologic process may involve predominantly the liver, the brain or the cornea. Obviously, any combination of these involvements may occur. In typical cases of Wilson's disease the predominant alterations appear within the extrapyramidal system and the liver. Since the cerebral manifestations are so striking, these cases are readily recognized; however, less typical cases occur in which there is predominant involvement of the liver or the cornea and hence may be entirely overlooked. For example, Lhermitte and Muncie,[21] reported 3 cases in which the patients were members of a single family in which the illness manifested itself chiefly as cirrhosis of the liver with actual hepatic dysfunction (urobilin and urobilinogen in urine, direct and delayed reactions in the direct van der Bergh test, icterus index 28.5, increased blood cholesterol). One of these patients had a typical Kayser-Fleischer ring. In none was there active evidence of involvement of the nervous system; however, on careful scrutiny there was noticed clumsiness of the hands, mild tremors of the upper extremities and slight incoordination of the limbs. Barnes and Hurst[14] studied a family in which cirrhosis of the liver developed in 4 members, and only 1 showed a Kayser-Fleischer ring. Two of these patients presented the typical appearance of Wilson's disease, while 2 showed no nervous manifestations. Histologically,

14. Barnes, S., and Hurst, E. W.: Brain **48**:280, 1925.
15. von Braunmühl, A.: Ztschr. f. d. ges. Neurol. u. Psychiat. **130**:1, 1930.
16. Bielschowsky, M., and Hallervorden, J.: J. f. Psychiat. u. Neurol. **42**: 177, 1931.
17. Richter, R.: J. Neuropath. & Exper. Neurol. **7**:1, 1948.
18. Eicke, W. J.: Arch. f. Psychiat. **114**:214, 1941.
19. Kuiper, F. C.: Over Haemachromatosis met Hepato-cerebral Degeneratie, Haarlem, J. Enschedé, 1932.
20. Spielmeyer, W.: Ztschr. f. d. ges. Neurol. u. Psychiat. **57**:312, 1920.
21. Lhermitte, J., and Muncie, W. S.: Arch. Neurol. & Psychiat. **23**:750, 1923.

in spite of the paucity of the clinical symptoms, lesions were found consistently within the lenticular nuclei and consisted of marked nerve cell damage associated with both progressive and regressive neuroglial alterations. Nerve cell changes also occurred within the cerebral cortex.

For some time there has been a great deal of confusion in the literature regarding the relationship of Westphal-Strümpell pseudosclerosis and Wilson's disease. Pseudosclerosis was first described by Westphal [22] in 1883, to include 2 cases in which the finding vaguely resembled the syndrome later described by Wilson. The patients had tremors of the limbs, rigidity, disturbance of speech and even attacks of unconsciousness. In none was the condition of the liver described. In 1899 Strümpell [23] revived this term to describe a condition observed in 3 patients, 2 of whom were syphilitic. None of Strümpell's cases resembled cases of hepatolenticular degeneration. In 1902, and later in 1912, Fleischer [7] described a greenish pigmentation of the cornea occurring in a patient with cirrhosis of the liver. His later paper, entitled "On a Hitherto Unknown Disease Related to Pseudosclerosis," includes for the first time the symptom complex of muscular rigidity, tremor, dysarthria and dementia, as well as corneal pigmentation. It is this paper that really gave impetus to the term "pseudosclerosis," which has been adhered to consistently, chiefly by the German writers. Actually, according to present definition, cases of pseudosclerosis are identical with cases of Wilson's disease; and it might be best to adopt the more descriptive term "hepatolenticular degeneration" originated by Hall [5] for both diseases.

The etiologic factors of hepatolenticular disease are quite obscure, but a brief review of possible etiologic factors might throw some light on this unusual liver-brain relationship. The following theories as to causation have been proposed:

1. That this disease is a hereditodegenerative process affecting both organs.
2. That the condition is acquired and the two organs are injured concomitantly by some endogenous toxin (Sjövall,[24] Löwy [25] and Braunmühl [10]).
3. That the condition is acquired but that the chief injury is to the liver, with the cerebral lesions being secondary to the hepatic injury (Kehrer,[26] de Lisi,[8] Pollak,[12] Brückner,[27] Weger and Natanson [28] and Lüthy [11]).

22. Westphal, C.: Arch. f. Psychiat. **14**:87, 1883.
23. Strümpell, A.: Ztschr. f. Nervenh. **16**:348, 1899.
24. Sjövall, E.: Acta path. Scandinav. **6**:193, 1929.
25. Löwy, J.: Deutsches Arch. f. klin. Med. **141**:213, 1922.
26. Kehrer, F.: Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:476, 1926.
27. Brückner: Jahrb. f. Kinderh. **110**:284, 1925.
28. Weger, A. M., and Natanson, D. M.: Arch. f. Psychiat. **88**:598, 1928.

4. That the condition is acquired and is secondary to the presence of some exogenous toxin.

Wilson and many other investigators have suggested that this illness may be acquired. They point out that prior to the appearance of the illness the patients and their families are normal physically and mentally. There is generally complete absence of any stigmas, such as congenital malformations, and no evidence of any constitutional defects. Furthermore, in its acuteness the illness is unlike any congenital illness. It would seem from a review of the literature that there still remains the possibility that this illness is some form of hereditodegenerative process in spite of the healthy family history and the rapid course. Certainly, similar sporadic appearances are seen in other conditions assumed at present to be degenerative.

From the etiologic standpoint the one constant feature is the presence of a damaged liver. This has led many investigators to the belief that the hepatic involvement precedes and is in a large part responsible for the cerebral lesions. Barnes and Hurst [14] felt that the primary factor was the hepatic damage. They expressed the belief that the liver became injured through a bacillary infection from the intestinal tract. They concluded that the disease of the liver was not chronic progressive cirrhosis but was the result of a series of attacks of acute hepatitis spaced over weeks or months. Occasionally the severity and the frequency of the hepatitis were sufficient to cause death before any nervous symptoms appeared.

The possibility of an exogenous toxin producing this disease has been emphasized through the work of Edsall and Drinker.[29] These investigators found that massive doses of certain metals, chiefly manganese chloride (10 to 60 mg.), produce selective damage in the liver and the brain. The liver shows parenchymatous degeneration amounting in some areas to necrosis. Mella [30] observed neuronal degeneration and glial reaction of the lenticular nucleus in monkeys inoculated with this metal.

HEMOCHROMATOSIS

Hemochromatosis is considered a true morbid entity characterized by generalized pigmentation of the skin, severe diabetes and enlargement with cirrhosis of the liver. The term was first used by von Recklinghausen,[31] in 1889, to indicate a histologic condition in which hemofuscin, as well as hemosiderin, was present in various body organs. Although the aforementioned three features characterize this disease, they do not

29. Edsall, D., and Drinker, C.: Contributions to Research, **1**:447, 1919.

30. Mella, H.: Arch. Neurol. & Psychiat. **11**:405, 1924.

31. von Recklinghausen, F.: Verhandl. d. Versamml. Gesellsch. f. Kinderh. deutsch. Naturf. u. Aerzte **62**:324, 1889.

consistently appear in each case and when present often vary in severity. For example, many cases have been reported in which the diabetes has been absent (Opie [32] and Osler [33]). The etiologic factors of this condition are still unknown, although Sheldon [34] felt that it was congenital and due to a fundamental disorder of the iron metabolism with accumulations of small amounts of pigment over a long period.

The first suggestion that there might be some relationship between hemochromatosis and Wilson's disease appeared in 1940, when Thaddea and Oettel [35] described pigmentation of skin and brain in a typical case of Wilson's disease. At autopsy the lenticular nucleus was small and pigmented. The nerve cells were decreased, and the glia was proliferated. The skin over the abdomen and the lower extremities showed increased pigmentation in the basal layers. No mention of diabetes was made in this case.

Even more striking were the cases of Brouwer [36] and Waggoner and Malamud.[37] Brouwer described a case in which both Wilson's disease and hemochromatosis were present clinically and pathologically. The patient, a 59 year old man, had bronzed skin, diabetes and cirrhosis of the liver. At the same time tremor of the hands developed with rigidity of the musculature, stiffness and difficulty of gait, dysarthria, dysphagia and increased emotionalism. At postmortem examination the usual signs of hemochromatosis were observed. The central nervous system showed parenchymal destruction with cavity formation in both putamens and in the caudate nucleus. Alzheimer cells were visible in scattered areas throughout the brain. Waggoner and Malamud described a classic case of hemochromatosis, but the cerebral symptoms were of a more diffuse nature, consisting of mental confusion, ataxia, hypertonia, facial palsy, dysarthria and reflex changes. At autopsy, aside from the hemochromatosis, there were widespread and severe lesions within the cerebral cortex, the putamen, the corona radiata, the globus pallidus, the red (or tegmental) nucleus, the cerebral peduncles and the cerebellar white matter. The lesions consisted of foci of status spongiosus with little glial reaction. Finally, Lewey and Govons [38] and Neumann [39]

32. Opie, E. L.: J. Exper. Med. **4**:279, 1899.
33. Osler, W.: Brit. M. J. **2**:1899.
34. Sheldon, F. H.: Haemochromatosis, London, Oxford University Press, 1935.
35. Thaddea, S., and Oettel, H. J.: Ztschr. f. d. ges. Neurol. u. Psychiat. **170**:552, 1940.
36. Brouwer, B.: Proc. Roy. Soc. Med. **29**:579, 1935.
37. Waggoner, R. W., and Malamud, N.: Tr. Am. Neurol. A. **67**:45, 1941.
38. Lewey, F. H., and Govons, S. R.: J. Neuropath. & Exper. Neurol. **1**:129, 1942.
39. Neumann, M. A.: J. Neuropath. & Exper. Neurol. **7**:19, 1948.

reported cases of hemochromatosis of the central nervous system. The patients showed no evidence of diabetes or of cirrhosis of the liver.

We, too, have had the opportunity of studying the nervous system in a typical case of hemochromatosis.

CASE 1.—The patient, a 62 year old man, became ill four years before his admission to the hospital. At the time of his admission there was bluish pigmentation of the hands and forearms, the face and the exposed areas of the neck and there was increased bronzing of the entire skin. Examination revealed the liver to be enlarged and firm. It was palpable 6 cm. below the costal margin. Laboratory examination of the urine showed sugar (4 plus). A dextrose tolerance test established a diagnosis of diabetes.

This patient was followed for four years. On his last admission he was weak, cachectic, incontinent and somewhat disoriented. The abdomen revealed no abnormality except for slight enlargement of the liver. During his hospital stay he became increasingly more stuporous. Neurologic examination showed scattered defects, with the left biceps jerk being greater than the right, but the right knee jerk being greater than the left. Gordon's reflex was present on the right. A lumbar puncture showed clear fluid under normal pressure; there were no cells. The blood urea nitrogen was 5 mg. per hundred cubic centimeters. Despite the treatment, the patient's course was rapidly downhill. Terminal studies of liver function gave essentially normal results.

At autopsy there was generalized bronzing of the skin. The liver weighed 1,835 Gm. Its external surface showed a fine nodular cirrhosis. On cut section the liver was firm and had a homogeneous brownish appearance. Histologic sections of the liver showed severe portal cirrhosis. In many areas the hepatic cells were atrophic and necrotic. External examination of the brain revealed a small amount of subarachnoid bleeding. The basilar vessels appeared normal. The rest of the brain showed nothing on gross examination.

Histologic examination of the brain revealed demyelination, which was chiefly perivascular in distribution, involving the entire cerebral hemispheres. The degree of demyelination was variable around different vessels. In some areas it was mild, with only swelling of the myelin sheaths. Around other vessels the myelin swelling and vacuolation extended for some distance away from the vessel and merged with similar areas around adjacent vessels. There were no fat granule cells in any of the areas of demyelination.

The cerebral cortex showed the same type of perivascular changes. In most areas the cortical involvement was not so extensive as that seen in the white matter and was localized chiefly to the inner cortical layers. The nerve cells appeared to have escaped any alteration with the exception of some of the cells in the inner two cortical layers, particularly those adjacent to areas of perivascular demyelination. Around these areas the nerve cells showed fairly extensive changes, consisting primarily of chromatolysis and absence of the staining properties. Many of the cells appeared to stain lightly, often only the outlines of the neurons being visible. Scattered neurons appeared shrunken, irregular and even fragmented.

The most extensive changes seen in this brain were localized within the hippocampal and calcarine regions. In these areas the white matter appeared to be almost completely destroyed and replaced by diffuse confluent areas of demyelination with actual cyst formation. Practically all the nerve cells within these regions showed destruction. The cells stained poorly, many being irregular and fragmented. In these regions only an occasional intact neuron could be

observed. In the region of the basal nuclei the thalamus appeared to be uninvolved. There was a most extensive destruction of the putamen and the globus pallidus. Here there was striking perivascular demyelination. The nerve cells also were extensively altered. Most of the larger cells were shrunken and stained poorly. In many cells the cytoplasm was fragmented, and that of some cells was entirely absent, leaving an isolated nucleus to indicate the previous presence of a normal nerve cell. Many ghost cells were also visible within the region of the globus pallidus. In the pons the changes were mild. There was definite granular ependymitis of the entire fourth ventricle. Within the pons the demyelination was limited primarily to the perivascular regions. Only occasional nerve cells showed some chromatolysis. No changes were observed within the region of the medulla.

ERYTHROBLASTOSIS FETALIS OR KERNICTERUS

This condition was apparently first described by Orth,[40] in 1875, at which time he reported a pathologic study of a jaundiced infant who died on the second day of life and showed at autopsy bilirubin crystals in the nuclear masses of the brain. This syndrome was first named kernicterus by Schmorl,[41] in 1902. During the past fifty years there have been many clinical and pathologic reports of this condition in which various neurologic symptoms have been described as complicating neonatal jaundice in infants from normal parents. Generally, the newborn infant becomes jaundiced within a few hours or a few days after birth and exhibits lethargy and drowsiness, together with a slight rise of temperature. Some infants are restless and show excessive crying with some rigidity or spasticity and even convulsive movements. Symptoms such as diarrhea, vomiting, irregular respirations and even circulatory collapse may occur. In many of the cases in which a child survives a milder form of the disease, it shows, after a period of a few weeks or even a few months, manifestations of a chronic neurologic involvement, namely, chorioathetotic movements, ataxia, rigidity, spasticity, convulsions, emotional instability and even mental retardation. Both in the acute and in the subacute or chronic stage the neurologic picture is most variable. The only consistent observation is that this illness occurs in infants who become jaundiced shortly after birth and whose parents are apparently normal.

For a long time the cause of this condition was unknown. It was regarded as an expression of intoxication due to dysfunction of the fetal liver or of the blood-forming organs. Some authors considered it the result of maternal intoxication. Real progress was made in the understanding of the illness by the discovery of the Rh factor by Landsteiner and Wiener.[42] The discovery of the role played by the

40. Orth, J.: Virchows Arch. f. path. Anat. **63**:447, 1875.

41. Schmorl, W.: Arch. f. Gynäk. **65**:504, 1902.

42. Landsteiner, K., and Wiener, A. S.: Proc. Soc. Exper. Biol. & Med. **43**:223, 1940.

Rh factor in intergroup hemolytic transfusion reactions (Wiener, Sonn and Hurst [43]) plus the observation that women who had such reactions often had stillbirths or erythroblastotic infants (Levine and his associates [44]) suggested that the Rh factor was the antigen in erythroblastosis fetalis. According to Levine and his associates, an "Rh negative mother" bearing an "Rh positive fetus" may become sensitized to the Rh factor. The Rh agglutinins thus produced pass back through the placenta, into the fetus, causing destruction of the blood of the fetus and giving rise to one or another manifestation of erythroblastosis. About 10 per cent of marriages involve a wife whose erythrocytes do not contain the Rh factor and a husband whose erythrocytes do contain it.

The clinical picture in erythroblastosis fetalis, or kernicterus, can be characterized as occurring primarily in infants that are apparently normal at birth, the labor being uncomplicated. The jaundice usually appears before the second day and is intense. Shortly after the appearance of the jaundice, there occurs evidence of involvement of the central nervous system, followed by a progressive illness, and death in a great many cases on or before the fifth day of life. Usually, one finds that more than one member of the family has had a similar type of involvement. The jaundice generally appears early, even a few hours after birth, but may be delayed as long as a number of days. In an occasional case the jaundice may not make its appearance until the infant is several weeks old. The jaundice increases rapidly and soon becomes intense. Symptoms suggestive of nervous system involvement are generally prominent and appear shortly after the onset of the jaundice, although in a few cases they may be delayed for two or three days or even weeks. These symptoms are chiefly spasticity of the extremities, opisthotonos, strabismus, spasms of the muscle, epileptiform attacks and, less commonly, a tendency toward drowsiness, apathy or even coma. Athetosis appears within a few weeks. The course is usually afebrile. The blood shows characteristic changes, anemia is present, and many erythroblasts are present. There is definite leukocytosis with reduction in the number of platelets. Death may occur wtihin a few days or weeks.

In cases in which the disease is of a milder type, the infants may survive. These children invariably show evidence of some residual damage of the nervous system, which may make its appearance after a period of several weeks, months or even years. Development, both mental and physical, is markedly delayed. Early there is often difficulty

43. Wiener, A. S.; Sonn, E. B., and Hurst, J. G.: Studies on Individual Differences in Human Blood and Their Practical Applications: Pathogenesis of Congenital Hemolytic Disease (Erythroblastosis Fetalis); III. Illustrative Case Histories of A-B Sensitization, paper no. 1, Brooklyn, New York, Weiner Laboratories, 1946.

44. Levine, P.; Katzin, E. M., and Burnham, L.: J. A. M. A. **116**:825, 1941.

in feeding, with little gain in weight. Movements become clumsy; there is no effort to speak and there is failure to sit up or even to hold the head erect. Walking and talking are retarded or never acquired. The gait frequently is spastic and unsteady. These children will often show marked incoordination in the use of the musculature (Paul,[45] Spieler,[46] Greenwald,[47] Guthrie [48] and Hart [49]). In most cases there are symptoms referable to the extrapyramidal system, namely, athetosis, tremor, choreiform movements and rigidity (Spieler [46] and Paul [45]). When spasticity develops, it is of varying distribution and may be present with hyperactive reflexes and toe signs. Subsequently in many children generalized convulsions develop (Hoffmann and Hausmann [50]). These convulsions may be of a focal or a generalized nature and may vary in frequency and severity. Almost all these patients will ultimately show some mental defect, such as emotional instability and intellectual retardation.

The autopsy findings are characteristic. In the acute form there is a distinct jaundice which can be found within the thalamus, the subthalamus, the lenticular nucleus, the caudate nucleus, the paraventricular gray matter, the hypothalamus and the dentate nucleus of the cerebellum. The jaundice is usually remarkably symmetric and is sharply localized to the gray matter. Within these jaundiced areas there is usually severe nerve cell damage which consists of chromatolysis, fragmentation and complete devastation of certain of the neurons (Schmorl,[51] Esch,[52] Beneke,[53] Hart [49] and Hoffmann and Hausmann [50]). Pigment is situated both within the injured cells and free in the interstitial tissues. Generally, the cerebral cortex has a normally preserved structure, but the individual cortical neurons often show both acute and chronic changes. Pigment is not found in the cortical elements. There is often a mild proliferation of glia. A few mononuclears may be seen within the leptomeninges. In the more chronic form of the disease the histopathologic changes are similar to those described in the acute form with the exception that the pigmentation often is not seen. In such cases the most severe damage again is found within the basal ganglions and in scattered areas throughout the cerebral cortex.

The cause of the pathologic changes in erythroblastosis has for a long time remained unknown. Early it was felt that kernicterus was a

45. Paul, S.: Arch. f. Kinderh. **74**:38, 1924.
46. Spieler, W. G.: Am. J. M. Sc. **149**:345, 1915.
47. Greenwald, H. M., and Messer, W.: Am. J. M. Sc. **174**:793, 1927.
48. Guthrie, L. G.: Proc. Royal. Soc. Med **7**:86, 1914.
49. Hart, C.: Berl. klin. Wchnschr. **54**:71, 1917.
50. Hoffmann, W., and Hausmann, M.: Monatschr. f. Kinderh. **33**:193, 1926.
51. Schmorl, W.: Verhandl. d. deutsch. path. Gesellsch. **6**:109, 1904.
52. Esch: Zentralbl. f. Gynäk. **32**:976, 1908.
53. Beneke: München. med. Wchnschr. **54**:2023, 1907.

primary necrosis of the brain, which subsequently became pigmented. Schmorl [51] expressed the belief that the necrosis within the basal structures was due to some toxin, perhaps bile or bile thrombi. Hart [49] also was of the opinion that poisoning or some other type of injury produced gradual degeneration of the ganglion cells, which then became impregnated with the bile pigment. Hoffmann and Hausmann [50] expressed the belief that the hepatitis caused liberation of some lipolytic substance which was responsible for the cerebral necrosis. They felt that there was a definite relationship between the severe disturbance of the liver and the pigmentation and necrosis of the ganglion cells in the basal nuclei, particularly since these cerebral changes occur only in cases in which definite necrosis of liver cells is observed. Wiener and Brody [54] in a very recent publication proposed the theory that the cerebral lesions in erythroblastosis fetalis result from the formation of agglutination thrombi in the vessels of the brain with simultaneous damage of the liver. They felt that the neurologic picture depended on the extent and the distribution of the original agglutination thrombi in the brain. The one difficulty with this theory is the specific localization of the lesions, in most cases, to the region of the basal nuclei. This specific localization of the lesions also suggests that there is an interrelationship between kernicterus and Wilson's disease. These two conditions have some similarity in view of the localization of the cerebral changes and their frequent association with hepatic lesions. However, Wilson's disease almost always occurs in adult life and is seldom associated with any jaundice or pigmentation of the cerebral tissues. Wiener and Brody [54] performed blood tests in cases of Wilson's disease and did not find any evidence of Rh sensitization.

A few of our cases of erythroblastosis fetalis will help illustrate some of the clinical and pathologic features of this illness.

Case 2.—A 5 month old boy was admitted to the hospital two days before his death because of severe jaundice that had been present since birth. Tests of the mother's, the infant's and the father's blood for an Rh factor revealed that the mother's blood contained none but that an Rh factor was present in the blood of the father and the child. The infant had marked respiratory distress with crowing respirations. According to the history, on the fourth day of life he had several convulsions and since then had shown signs of spasticity. He had been nourished on subcutaneous fluid since birth and had gained little weight. The physical examination revealed an extremely thin, small child lying in opisthotonos, with the extremities appearing mildly spastic. The respirations were noisy, and there was mild dyspnea. The clinical impression at the time of admission was erythroblastosis fetalis with possible cerebral damage. A pneumoencephalogram was made shortly after his admission. It showed cerebral atrophy and questionable external hydrocephalus. The child's temperature continued to rise, and he died a few days after admission to the hospital.

54. Wiener, A. S., and Brody, M.: Am. J. Ment. Deficiency **51**:1, 1946.

An autopsy examination of the brain revealed prominent perivascular congestion. Coronal sections of the right cerebral hemisphere revealed some congestion but showed normal structure and normal basal nuclei.

Microscopic sections through the brain showed moderate vascular congestion with a few scattered perivascular hemorrhages. The most striking changes were limited to the nuclear structures of the basal ganglions and the cortex. Many of the cortical neurons, particularly in the inner cortical layers, showed a most severe disruption of the normal cell arrangement. The nerve cells were chromatolytic and often fragmented. Most of the cells stained poorly. In the basal ganglions only the large cells of the globus pallidus showed severe changes. Most of the cells were fragmented and were surrounded by large clear areas in this region. Often only a small fragment of the cell body still remained attached to a fairly intact nucleus. Some of the neurons showed more acute changes and were swollen and chromatolytic. The cells of the putamen were less severely involved. There was an occasional perivascular area of myelin swelling and early demyelination, particularly in the cortical and subcortical areas. Scattered areas of glial increase and even an occasional glial nodule were observed.

Case 3.—A 6 day old white girl began to have a yellow tinge to the skin on the third postnatal day and was given 25 cc. of whole blood intramuscularly. From that time on the progress was gradually downhill. She died on the sixth day.

Autopsy revealed a fairly well nourished, full term infant. The right and left pleural cavities each contained 25 cc. of yellow fluid. Gross examination of the brain revealed slight congestion and mild greenish pigmentation. Coronal sections showed mild diffuse discoloration with definite pigmentation of the basal nuclei, most marked in the globus pallidus and the putamen. There was similar pigmentation along the hippocampal gyrus, the tegmentum of the brain stem, the olives and the dentate nucleus.

Histologic section through the brain showed marked congestion of the cerebral cortex with little other change. The neurons and the myelin seemed to be uninvolved. The most severe alterations occurred within the globus pallidus, where there were definite cell changes. These consisted chiefly of severe swelling and chromatolysis. Many of the cells had lost their staining properties and appeared as ghost cells. There was slight fragmentation of the cell processes as well as of the cell body.

Histologic section of the liver showed severe atrophy and destruction of the liver cords. There was a large number of nucleated red cells filling the liver sinuses.

EXPERIMENTAL STUDIES

The diseases covered thus far offer little information as to the possible causes of the cerebral lesions. In all these illnesses there was damage of both liver and brain. There is a possibility that these combined involvements may be coincidental and that the damage of the liver is not related to the cerebral changes. There are numerous experimental studies that offer some information regarding the possible interrelationship of hepatic and cerebral disease. As early as 1893, Hahn and his associates [55] produced nervous symptoms in dogs by the use of Eck's fistula and a meat

55. Hahn, M.; Massen, O.; Nencki, M., and Pawlow, J.: Arch. f. exper. Path. u. Pharmakol. **32**:161, 1893.

diet (the Eck fistula served to eliminate the liver metabolism by connecting the portal vein with the vena cava and thus allowing the blood carrying chemical products from the intestine to pass directly into the main blood circulation and reach the nervous system).

Fuchs [56] in 1921, using the same method, also produced cerebral involvement in dogs, manifested as ataxia, tremors, twitchings and coma. Histologically, these animals showed evidence of a cellular reaction which was interpreted as encephalitis. Fuchs then fed cats guanidine hydrochloride and produced similar cerebral symptoms. He felt that the Eck fistula allowed the strongly toxic guanidine to reach the circulation, evading the liver. In England similar studies were done by Findlay.[57] Silberstein [58] in 1924, by using Eck's fistula, also succeeded in producing in dogs an encephalitis resembling epidemic encephalitis. He was able to transmit the cerebral involvement to dogs or rabbits by subdural and corneal inoculation of the filtrate of emulsified brain. In these animals there was a question of some latent virus being actuated by the process.

In 1932 Baló and Korpássy [59] produced marked cerebral involvement in 6 of 8 dogs by restricting them to a one-sided meat diet after Eck's fistula had been established. These dogs showed apathy, uncertain gait, hypotonia, amaurosis, catalepsy, convulsions, fibrillary twitchings and finally coma. The authors were unable to transmit the encephalitis to other dogs and therefore felt that there was no evidence that the encephalitis of dogs with Eck's fistula was caused by a living microorganism. They regarded the encephalitis as an intoxication due to the exclusion of the liver. If the intoxicated dogs do not eat, the toxic symptoms disappear only to reappear after the dog begins to eat. In fatal cases there are mild changes localized chiefly to the caudate nucleus.

Crandall and Weil [60] in 1933 produced hepatic changes in dogs by ligation of the common bile duct or the pancreatic duct or by making Eck's fistula. They then obtained serum from these animals and incubated it with rats' spinal cord for twenty hours at 37 C. Beginning at the fourth day, the dogs' serum contained substances which were destructive to the rats' spinal cord in vitro. These substances were not lipases. The brains of the dogs showed spongy necrosis of the ventricular wall, diffuse nerve cell damage, demyelination and glial proliferation. These investigators felt that the cerebral damage was produced by a toxin. Finally de Jong [61] in an extensive publication on catatonia did much to further

56. Fuchs, A.: Wien. med. Wchnschr. **71**:709, 1921.

57. Findlay, A. M.: Brit. J. Exper. Path. **5**:92, 1924.

58. Silberstein, F.: Wien. klin. Wchnschr. **37**:30, 1924.

59. Baló, J., and Korpássy, B.: Arch. Path. **13**:80, 1932.

60. Crandall, L. A., and Weil, A.: Arch. Neurol. & Psychiat. **29**:1066, 1933.

61. de Jong, H. H.: Experimental Catatonia, Baltimore, William & Wilkins Company, 1945, p. 132.

present knowledge as to the possible relationship of hepatic and cerebral damage. The author ligated the hepatic artery in 24 cats and noticed cerebral symptoms only in the 16 showing damage of the liver. Ligation of the renal and splenic arteries with resulting renal and splenic necrosis produced no cerebral symptoms. Dogs with Eck's fistula presented definite catatonia. De Jong, from his studies, felt that the cerebral damage is the result of a toxin liberated by the intestine and normally removed by the liver. In the liver damage and Eck's fistula such toxins are not removed and hence damage the brain. He did not feel that the process was due directly to poisoning from destruction of liver tissue itself.

HEPATIC DISEASE IN MAN

If cerebral damage actually results from the failure of the liver to detoxify the blood, then damage of the brain should be seen in some of the many persons suffering from severe hepatic disease. Little literature is available concerning such findings. Waggoner and Malamud [87] reported 5 cases in which ordinary hepatic disorder was associated with scattered proliferative changes of the astrocytes. In view of the paucity of material on this subject it was felt of value to study the central nervous system in 18 cases of acute, subacute and chronic disease of the liver. In all these cases the clinical history revealed only terminal evidence that the nervous system was involved, and this evidence consisted only of terminal lethargy or coma. In 8 of the cases the nervous system showed extensive changes. The alterations involved both the gray and the white matter and were at times limited to the nerve cells and at other times to the myelin elements. The demyelination was predominantly perivascular and involved both gray and white matter. In some cases it was so severe as to produce large demyelinated plaques that eradicated all underlying tissue elements. Fat granule cells were not present. None of the injured areas showed any cellular reaction. The neurons were irregularly damaged. Scattered nerve cells showed irregular chromatolysis, vacuolation and even fragmentation. Many failed to stain and appeared as ghost cells. Within the basal nuclei the most severe damage occurred in the putamen and the globus pallidus. The brain stem showed little alteration.

A few illustrative cases may serve to demonstrate the variation in cerebral involvement in cases of hepatic disease.

CASE 4.—This patient was a 6½ week old girl. Three weeks before admission the mother noticed that the baby was becoming jaundiced. On admission the infant was well developed and well nourished, and markedly jaundiced. The liver was palpable about 3 cm. below the costal margin in the midclavicular line. The spleen was also palpable. The blood on admission showed a hemoglobin content of 12.8 Gm.; the leukocyte count was 16,300. The bilirubin content of the serum in one minute was 6.6 mg., with a total of 10.5 mg., per hundred cubic centimeters. Thymol turbidity was 1 unit. The cephalin-cholesterol

flocculation test (Hanger's test), was negative at twenty-four and forty-eight hours. The blood cholesterol was 252 mg. per hundred cubic centimeters. Quantitative determination of urobilinogen in the urine revealed none, and less than 3 Ehrlich units per hundred grams was found in the stool.

Two weeks after the patient was admitted to the hospital, severe diarrhea suddenly developed with an elevation of temperature (102.8 F.). The hemoglobin content of the blood was found to be 8.9 Gm. per hundred cubic centimeters, with a red cell count of 2,350,000. An exploratory laparotomy was performed. The common duct was not found, but when methylene blue was injected into the gallbladder apparently some methylene blue was caused to go into the intestines through the common duct. The patient was discharged three weeks after admission.

A week before her last admission there developed a gradual protuberance of the abdomen. She became more irritable and began to refuse feedings. She appeared to be in definite discomfort. She scratched at accessible areas of the skin constantly. Respirations were labored. There was marked generalized icterus which had a deep green-bronze tint and involved the scleras and the mucous membranes. Many spider telangiectases were present about the scar of the previous operation in the right upper quadrant of the abdomen. Other spider nevi were also found. The liver was palpable as a firm, stony-hard mass extending 8 cm. down to the right midclavicular line. Shortly after this admission the patient's temperature began to rise; she became lethargic. She had voluminous hemorrhages by rectum, the respirations became progressively more shallow, and she died two days after admission.

Autopsy revealed a seriously malnourished, jaundiced child. The liver weighed 360 Gm. and was green, hard and finely nodular. Scattered throughout the liver, but particularly along the major portal vessels, were nodular areas that were dark green and quite soft. Histologic sections showed marked cirrhosis of the portal type. There was proliferation of the bile ducts, each of which was filled with a plug of inspissated bile. The hepatic ducts could not be found, and it was suspected that there was a congenital atresia of the hepatic ducts.

External examination of the brain showed scattered areas of light brown pigmentation over the cerebral hemispheres. Histologic sections revealed severe involvement of the entire central nervous system. The most striking alteration consisted of scattered areas of perivascular demyelination involving primarily the white matter and the inner cortical layers. This condition was most severe in the anterior parts of the cerebral hemispheres, primarily in the temporal, parietal and frontal areas. In many of these areas demyelination was fairly complete, producing a vacuolated or cystic appearance. Even in the areas of more diffuse destruction of myelin, one could detect a perivascular arrangement of the tissue injury.

The cortical neurons, particularly those in the inner two cortical layers, showed a variable degree of alteration. Many of the cells were shrunken, others were vacuolated, and still others showed definite fragmentation of the cell and body processes. The basal nuclei showed changes similar to those of the cerebral hemispheres. In these nuclei the demyelination was both focal and diffuse. The areas of more diffuse tissue injury were large and showed signs of early breakdown and vacuolation of tissue. The nerve cells throughout both the thalamus and the globus pallidus were severely injured. They showed diffuse chromatolysis and beginning fragmentation of the cell bodies. The medulla appeared unaltered. In the cerebellum there was a fairly extensive demyelination of the white matter. The granular layer of the cerebellum was narrowed, with

breakdown and vacuolation of tissue. The nerve cells throughout both the thalamus and the globus pallidus were severely injured. They showed diffuse chromatolysis and beginning fragmentation of the cell bodies. The medulla appeared unaltered. In the cerebellum there was a fairly extensive demyelination of the white matter. The granular layer of the cerebellum was narrowed, with many cells being absent. The Purkinje cells were reduced in number, and many showed marked alteration with fragmentation of the cell processes and marked irregularity of the cell outline.

Comment: In this case the patient suffered progressive cirrhosis of the liver secondary to atresia of the hepatic duct. Autopsy studies showed severe, widespread damage of the entire brain with no tendency to localize in any particular region. The changes seen in the brain were extremely similar to those described by me in a case of hemochromatosis in which cirrhosis also occurred. It certainly would appear that severe chronic damage of the liver can in many cases result in widespread injury of the brain.

CASE 5.—A 53 year old woman gave a six months' history of jaundice and loss of weight. She was obese and deeply jaundiced. The liver was palpable but not tender. Laboratory studies revealed a hemoglobin content of 9.8 Gm. per hundred cubic centimeters, with 3,471,000 red cells. The prothrombin time was 26.2 seconds against a control of 14.6 seconds. Blood urea nitrogen was 14 mg. per hundred cubic centimeters. Serum bilirubin was 16.3 mg. in one minute, with a total of 29.5 mg., per hundred cubic centimeters; these levels gradually rose to 26.7 mg. and 44.3 mg. before death. Thymol turbidity was 10 units, cephalin-cholesterol flocculation was 4 plus, and urinary urobilinogen was 45.8 mg per day.

In spite of therapy her course was downhill. Her jaundice deepened, and she became drowsy. She finally passed into a deep coma and died within ten days after admission.

At autopsy the liver weighed 1,320 Gm. It was nodular and yellowish. On cut section little recognizable tissue was present between the nodules. Histologic sections showed moderate portal fibrosis. In some areas hepatic cells were swollen and the cords disrupted. Frank necrosis was seen in a few places.

The entire brain showed most extensive involvement. Large areas of both gray and white matter were completely destroyed, leaving large demyelinated plaques. The tissue injury had a perivascular arrangement even in the more extensive areas of diffuse destruction of myelin. In those regions where the injury was less severe, there had occurred rather typical perivascuar demyelination of varying degree and extent. There was no evidence of any inflammatory reaction. The vessels, though surrounded by altered tissues, revealed no changes even with special stains.

The cortex showed a similar but less severe perivascular involvement. Practically every vessel was surrounded by an area of myelin loss. The neurons were less severely damaged. Scattered nerve cells showed irregular chromatolysis. Many stained poorly and appeared as ghost cells. Generally the cell nuclei were uninvolved.

The basal nuclei also had undergone uniform and extensive perivascular demyelination. The nerve cell damage was most severe within the putamen and

the globus pallidus. The nerve cells within the thalamus were surprisingly intact in spite of an extensive perivascular demyelination. Sections through the brain stem showed little tissue change.

Comment: In this case the patient suffered from subacute atrophy of the liver. The lesions of the brain were actually identical with, but more severe than, those in the previous case in which the illness was chronic. The involvement of the brain was so severe that in many areas the demyelination resembled that seen in multiple sclerosis. The predominant perivascular nature of the lesions certainly suggests that the cerebral damage is secondary to the presence of some toxin which reaches the brain through the vascular system.

GENERAL COMMENT

In evaluating the significance of the cerebral lesions observed in cases of hepatic disease, one must take into account the actual cause of the hepatic involvement. Within recent years there has been an increasing tendency to relate many of the subacute and chronic involvements of the liver to an original infectious or epidemic hepatitis(Lucké,[62] Wood,[63] Turner [64] and Cockayne [65]). Since at present it is accepted that infectious hepatitis is caused by a virus which can be transmitted by the oral route (Havens,[66] Neefe and co-workers [67] and Findlay and Martin [68]), the question arises whether the cerebral alterations in cases of hepatic disease are perhaps the direct result of the brain's being invaded by the causative infective agent. It is known that in patients with severe hepatic disease definite cerebral symptoms do occur. Such patients occasionally become lethargic and even comatose. Extensive focal symptoms may appear, such as muscular rigidity, hemiplegia, hemianopsia and parkinsonian syndromes (Lucké [62]). However, in the fatal cases of infectious hepatitis, the cerebral changes, as would be expected, resemble those of an acute virus disease. The brain shows definite lymphocytic infiltration around the vessels in the meninges, the brain stem, the paraventricular system and the basal nuclei. The ganglion cells are regularly involved and show severe damage with complete destruction. Diffuse petechiae are common, and in the occasional case large hemorrhages may cause extensive injury of tissue.

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62. Lucké, B.: Am. J. Path. **22**:471, 1944.
63. Wood, D. A.: Arch. Path. **41**:345, 1946.
64. Turner, R. H.; Snavely, J. R.; Grossman, E. B.; Buchanan, R. N., and Foster, S. O.: Ann. Int. Med. **20**:193, 1944.
65. Cockayne, E. A.: Quart. J. Med. **6**:1, 1912-1913.
66. Havens, W. P., Jr.: J. A. M. A. **126**:782, 1944.
67. Neefe, J. R.; Stokes, J., Jr.; Reinhold, J. G., and Lukens, F. D. W.: J. Clin. Investigation **23**:836, 1944
68. Findlay, G. M., and Martin, N. H.: Lancet **1**:678, 1943.

These lesions obviously do not resemble those seen in our cases, and one is forced to look elsewhere for a clarification of the pathologic observations. By far the most information is obtained from a review of the experimental studies, which seem to indicate definitely that the cerebral lesions are the result of the damage to the liver. When the liver is sufficiently damaged, it apparently allows the various intestinal toxins to reach the systemic circulation and thus to injure the brain. The exact nature of this endogenous toxin is at present unknown, but experimentally it appears to be related in some way to a high protein intake. Since this toxin is disseminated through the blood stream, one would expect the cerebral lesions to be widely disseminated throughout the brain and to have a perivascular arrangement. This is exactly what was observed in our cases and certainly lends evidence to this concept. Just why such cerebral damage is not found in every case of severe disease of the liver is not known. Certainly, the incidence of positive findings will increase with more careful study.

SUMMARY

Ever since Gower's first description of chorea associated with cirrhosis of the liver, in 1888, it has been apparent that severe disease of the liver may be accompanied by widespread cerebral involvement.

Wilson's disease comprises the best known of these hepatocerebral involvements. Many investigators feel that the hepatic damage is the most important component of this illness and may prove fatal for the patient before severe cerebral symptoms appear. Even Wilson felt that this disease was acquired and probably toxic in nature.

Hemochromatosis, which is characterized by pigmentation of the skin, diabetes and cirrhosis of the liver may also result in widespread cerebral lesions resembling those seen in Wilson's disease.

Experimental studies show that when the liver is damaged by ligation of the hepatic artery or is by-passed by means of an Eck fistula, severe cerebral damage results. These studies suggest that the lesions of the brain are the result of the action of a toxin liberated by the intestine and normally removed by the liver.

In our series of 18 cases of acute, subacute and chronic disease of the liver, cerebral damage was observed in 8 cases. The alterations involved both the gray and the white matter and were predominantly perivascular in nature. The widespread and perivascular distribution of the lesions again suggests that hepatic damage, if severe, apparently allows some toxin to reach the systemic circulation and thus to injure the brain. The nature of this endogenous toxin is at present unknown.

Notes and News

Appointments.—W. C. Thomas, assistant professor of pathology in Wake Forest College, Winston-Salem, N. C., has been appointed associate professor of pathology in Temple University, Philadelphia.

Death.—Edward R. Stitt, Rear Admiral, United States Navy, retired, died Nov. 13, 1948, aged 81. He was commissioned assistant surgeon in the medical corps of the Navy in 1889. He was a great teacher of bacteriology and of tropical diseases. The tenth edition of his "Practical Bacteriology, Hematology and Parasitology" appeared recently. His "Diagnostics and Treatment of Tropical Medicine" is a well known authority in its field. In 1945 he was awarded the Richard Pearson Strong Medal for outstanding service in tropical medicine.

Awards.—The second Francis Amory Prize of the American Academy of Arts and Sciences, a septennial award of $21,000 for outstanding work in the alleviation or cure of urologic disorders, first made in 1940, will be equally divided among the following: Charles B. Huggins, of the University of Chicago; S. A. Waksman, of the New Jersey State Agricultural Experiment Station; G. N. Papanicolaou, of the Cornell University Medical College; A. B. Gutman, Presbyterian Hospital, New York; W. J. Koff, Holland, and G. F. Marian, Scotland.

George N. Papanicolaou, professor of clinical anatomy in the Cornell University Medical College, New York, has received the Borden Prize of the Association of American Medical Colleges for his work on the detection of cancer by cytologic examination. The Borden Prize is awarded for outstanding work in medical science by a faculty member of an American medical school.

The Ward Burdick Award of the American Society of Clinical Pathologists was given to P. R. Cannon, Chicago, for his contributions in the field of pathology.

Society News.—At the twenty-seventh annual meeting of the American Society of Clinical Pathologists in Chicago, Oct. 12 to 15, 1948, O. A. Brines, Detroit, was inducted as president, J. B. McNaught, Denver, was made president-elect and C. H. Manlove, Portland, Ore., was elected vice president. C. G. Culbertson, Indianapolis, was appointed secretary-treasurer on the resignation of A. S. Giordano, South Bend, Ind. The annual meeting of the American Association of Pathologists and Bacteriologists will be held in Boston April 15 and 16, 1949.

The Chicago Medical School Approved.—The American Medical Association and the Association of American Medical Colleges have granted full approval to the Chicago Medical School, bringing the number of medical schools in Chicago to 5 and the number in the United States to 71.

Cancer Research.—The official organ of the American Association for Cancer Research, previously published by the Ann Arbor Press, will now be published by the University of Chicago Press under the editorship of Paul E. Steiner, professor of pathology at the university.

Books Received

THE RH BLOOD GROUPS AND THEIR CLINICAL EFFECTS. By P. L. Mollison, A. E. Mourant and R. R. Race. Medical Research Council Memorandum no. 19. Pp. 74. Price 1s., 6d. London: His Majesty's Stationery Office, 1948.

The booklet is divided into three parts: the Rh groups (Race), clinical considerations (Mollison) and Rh testing (Mourant). The British classification of the Rh types with the Fisher-Race terminology is presented clearly with the help of tables and diagrams. Those who are interested in the current controversy concerning the respective merits of the Fisher-Race and the Wiener terminology will find here a well condensed presentation of one of the two points of view.

The clinician will find in Mollison's chapter a summary of practical applications to obstaetric and pediatric practice. One could take exception to a statement on page 39: ". . . the possibility of making a presumptive diagnosis of the disease in the infant by simply testing the mother's serum for the presence of Rh antibodies has made the ability to recognize the disease from post-mortem appearances far less important than formerly." This statement is symptomatic of a tendency to neglect anatomic and microscopic studies and to depend entirely too much on serologic findings for the diagnosis of fetal erythroblastosis. There is good reason to deplore this trend. On the contrary, careful autopsies with thorough microscopic examinations are just as important now as they have ever been if physicians are to avoid the error of lumping together entirely unrelated conditions. In keeping with the preceding criticism is the cursory treatment of pathologic anatomic aspects of erythroblastosis.

The third chapter is a well written digest of Rh technics. Those who are engaged in Rh studies will second Dr. Mourant's suggestion: "It should be appreciated by patients, doctors, and technicians alike that anyone who makes use of Rh tests is under an obligation to do everything possible to keep up supplies of both common and rare sera, lack of which is even now holding up . . . research."

The booklet can be recommended as one of the best reviews of the steadily expanding and complex field of Rh.

CORRECTION

In the June 1948 issue of the ARCHIVES OF PATHOLOGY, an obituary of Professor Bonne appeared on page 795. In it the statement was made, "Dr. Bonne spent the occupation years in Australia, returning to Java after the war."

We are now advised that the statement just quoted is incorrect and that Professor Bonne spent the occupation years in a Japanese concentration camp, where he was a great help and a source of inspiration to his fellow prisoners, several of whom have recently been seen by our informant.